2302774 – Advance Organic Synthesis

Lecture 4

Protecting Groups

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Recommended Textbook:

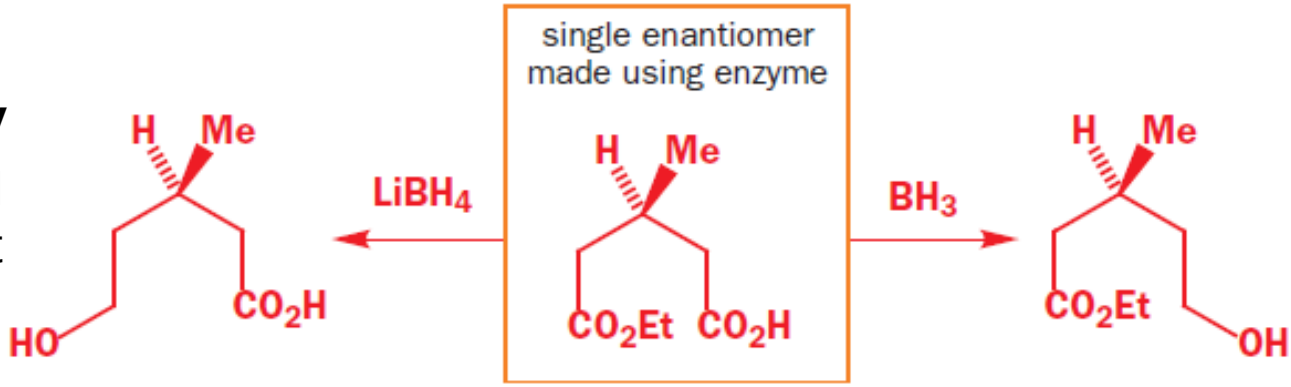
Chapter 24, 25 and 49 in *Organic Chemistry*, 1st Edition, J. Clayden, N. Geeves, S. Warren, **2001**, Oxford University Press

Chemoselectivity

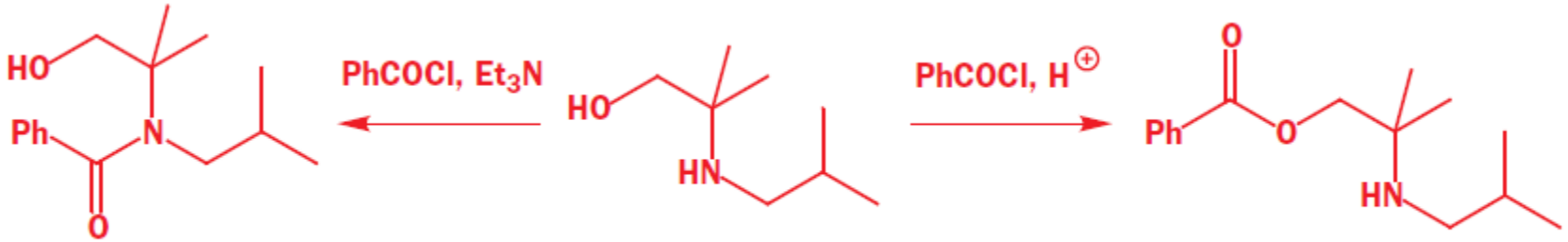
One functional group may be more reactive than another for **thermodynamic** or for **kinetic** reasons

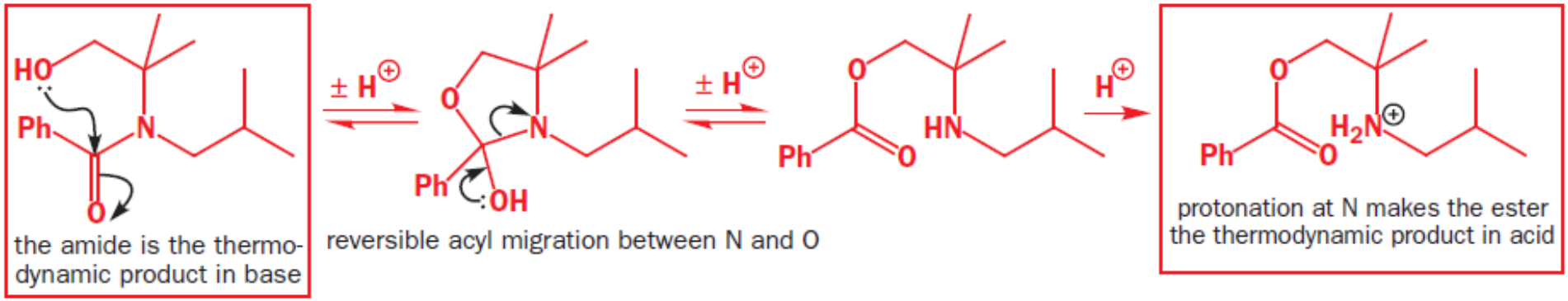
Kinetic chemoselectivity

Reaction at one functional group is faster than at another



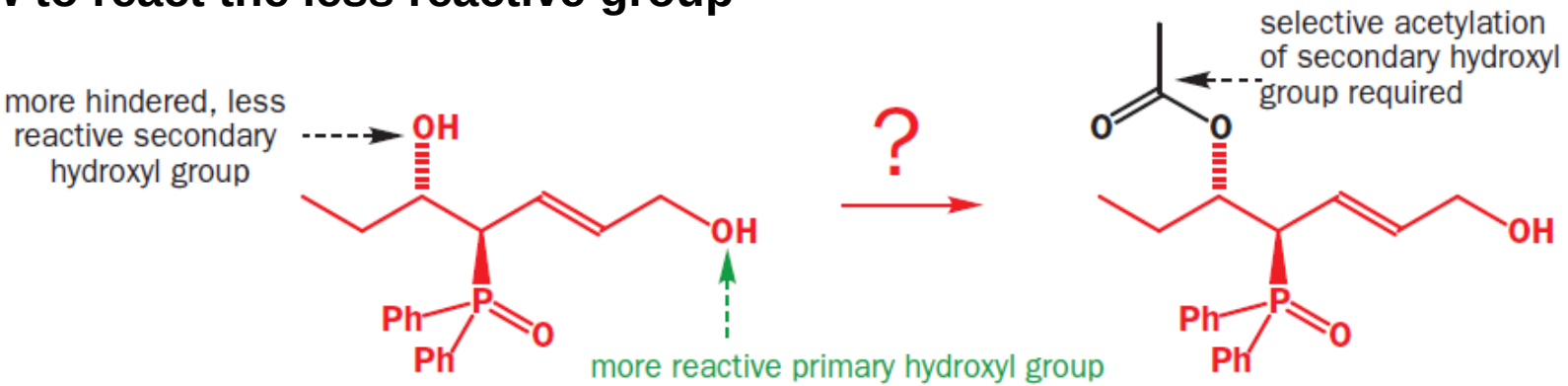
Thermodynamic chemoselectivity



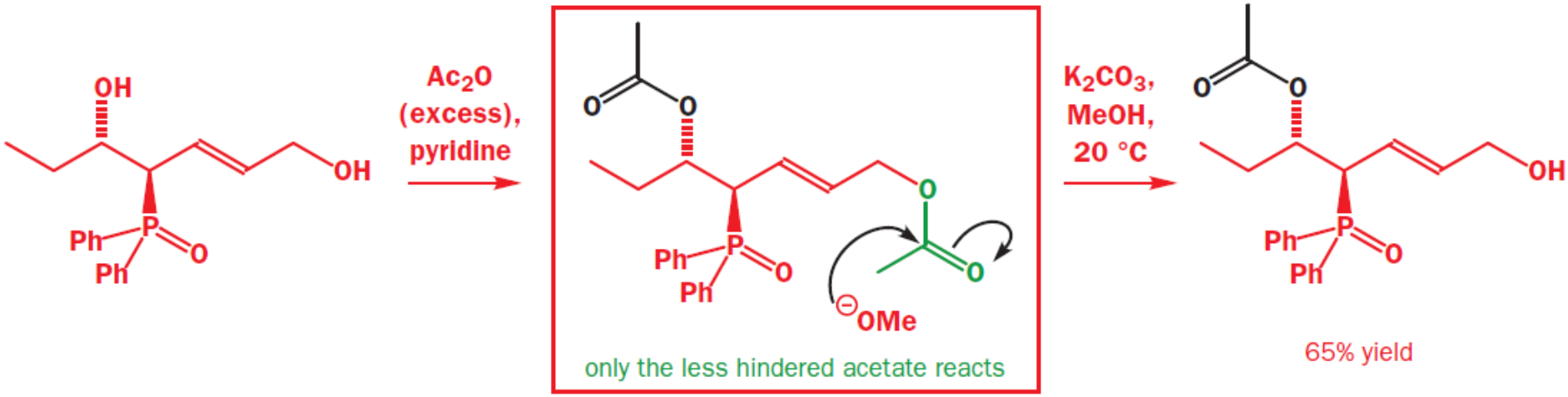


Chemoselectivity

How to react the less reactive group

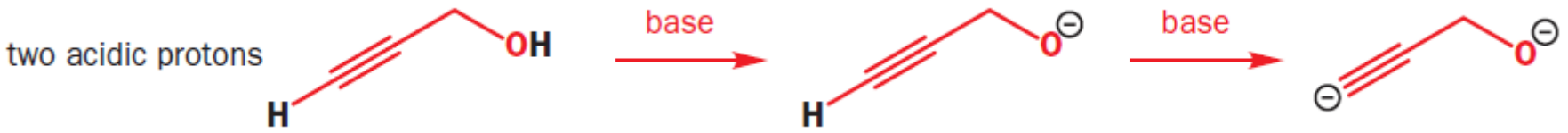


Acetylated **both** hydroxyl groups, and then treated the bis-acetate with mildly basic methanol, which reacted only at the **less hindered** acetoxy group



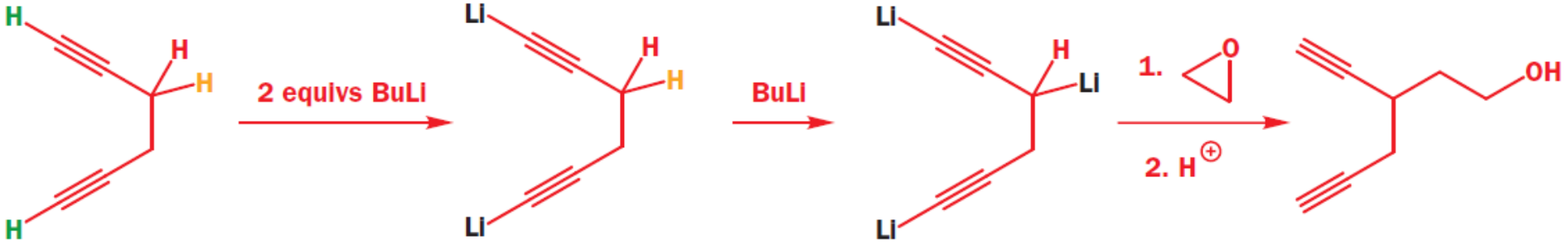
Chemoselectivity

How to react the less reactive group - Dianions



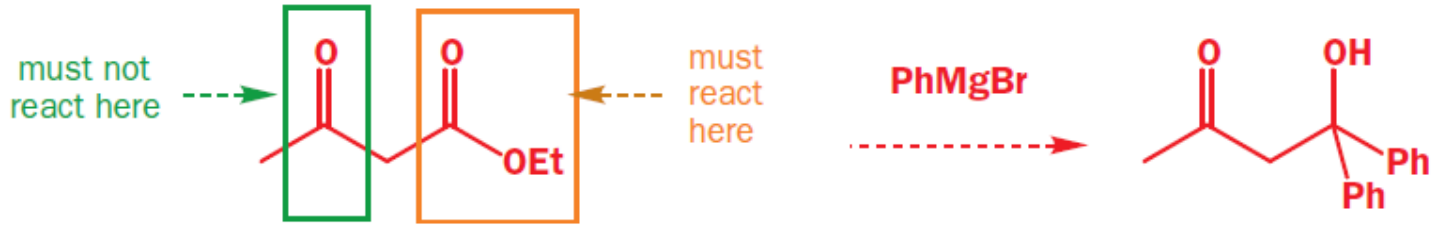
1-Propynol can be **deprotonated twice** by strong bases—first, at the hydroxyl group to make an alkoxide anion (pKa 16) and, secondly, at the alkyne (pKa 25) to make a '**dianion**'

When this dianion reacts with electrophiles it always reacts at the **alkynyl anion** and not at the alkoxide – **the anion that is formed last reacts first**

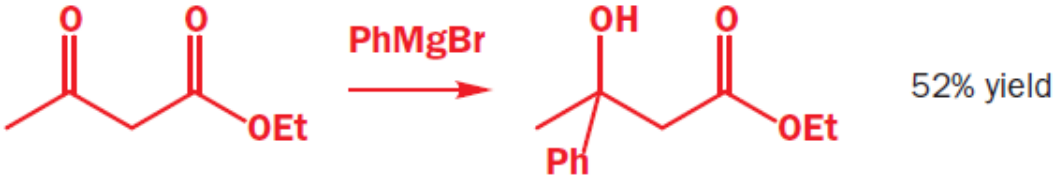


Chemoselectivity

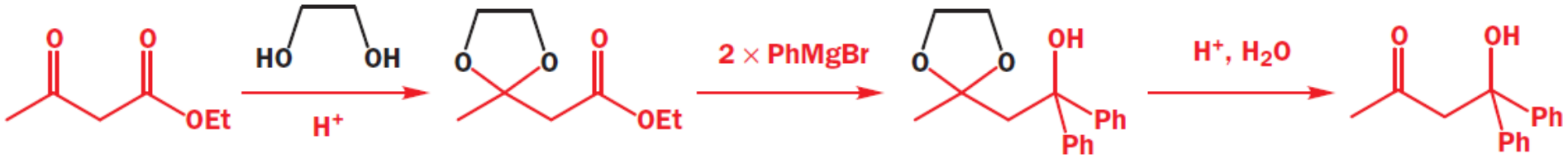
How to react the less reactive group – Protecting Groups



This tertiary alcohol could be made from a keto-ester if we could get phenylmagnesium bromide to react with the **ester rather than with the ketone**

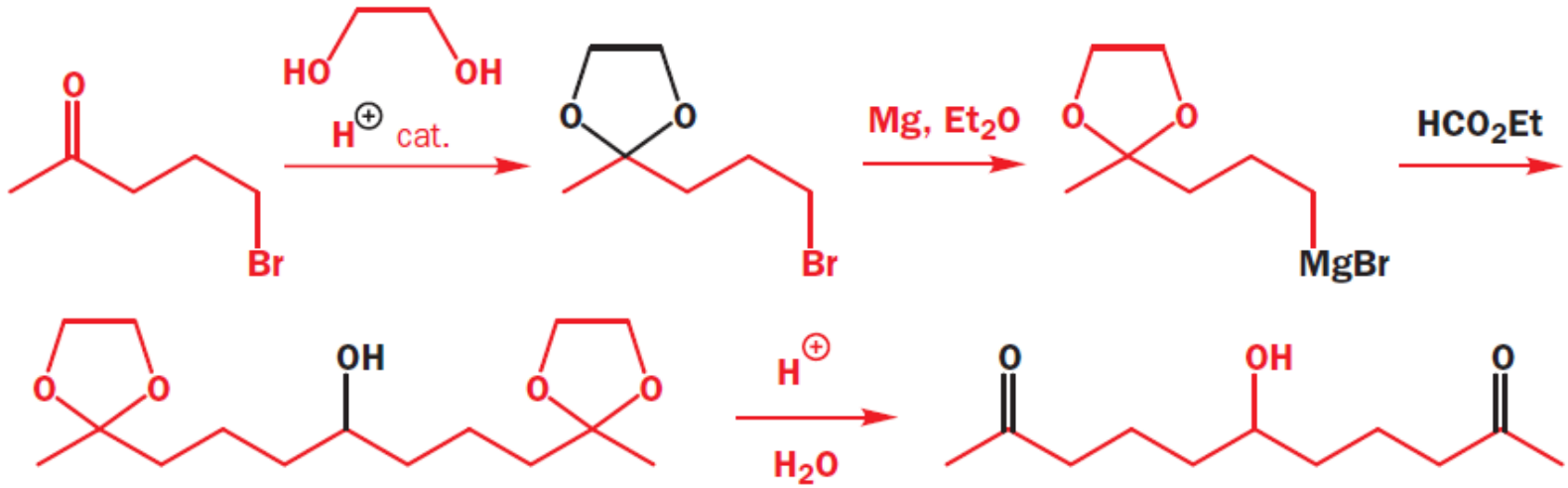


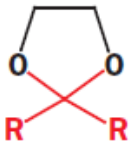
acetal is an ideal choice here – acetals are **stable to base** (the conditions of the reaction we want to do), but are **readily cleaved in acid**



Carbonyl Protecting Groups – Acetal

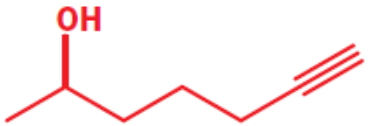
One way to make it is to add a Grignard reagent twice to ethyl formate. But, of course, a **ketone containing Grignard** is an impossibility as it would self-destruct, so an acetal-protected compound was used.

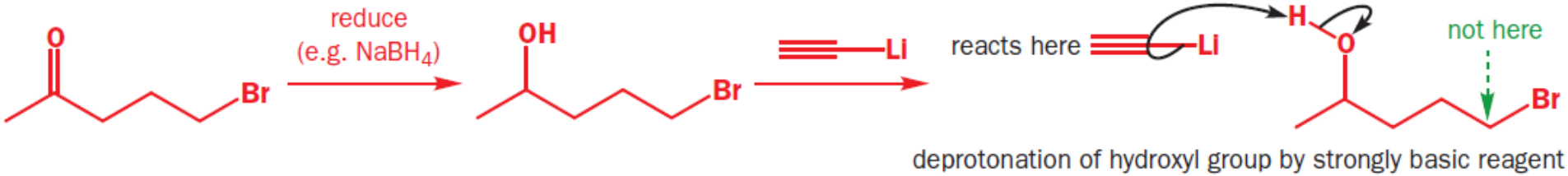


Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H^+ cat.

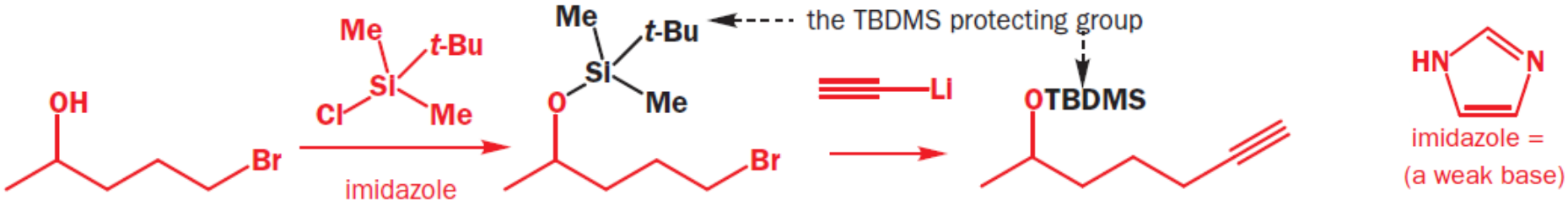
Alcohol Protecting Groups – Silyl ether

Strongly nucleophilic reagents like Grignard reagents and organolithiums are also strong bases, and may need **protecting from acidic protons**

Target molecule: 



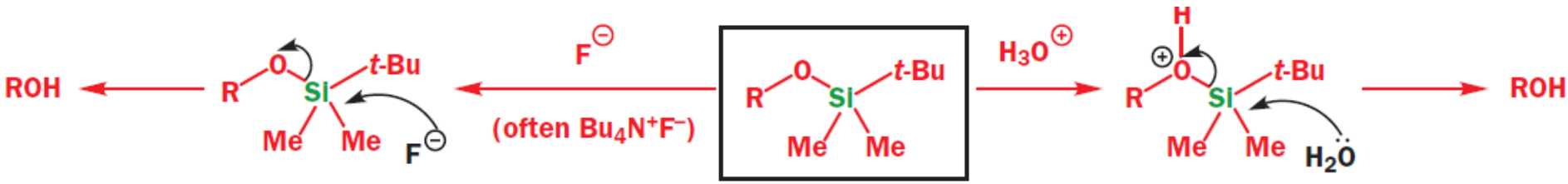
protect the hydroxyl as a silyl ether, using **trialkylsilyl chloride** in the presence of a **weak base**, usually imidazole, which also acts as a **nucleophilic catalyst**



Alcohol Protecting Groups – Silyl ether

Silicon has a strong affinity for **electronegative elements**, particularly O, F, and Cl, so trialkylsilyl ethers are attacked by hydroxide ion or fluoride ion but are more **stable to carbon or nitrogen bases or nucleophiles**

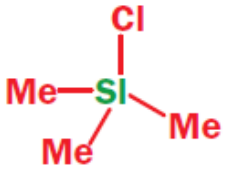
They are usually removed with aqueous acid or fluoride salts, particularly **$Bu_4N^+F^-$** which is **soluble in organic solvents**



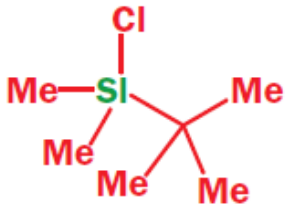
The **relative stability** to nucleophiles is determined by the t**hree alkyl groups carried by silicon**; the most labile, trimethylsilyl (TMS), is removed simply on treatment with methanol, while the most stable require hydrofluoric acid

Protecting group	Structure	Protects	From	Protection	Deprotection
trialkylsilyl (R_3Si-, e.g. TBDMS)	RO—$SiMe_3$ RO—$SiMe_2Bu^t$	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-

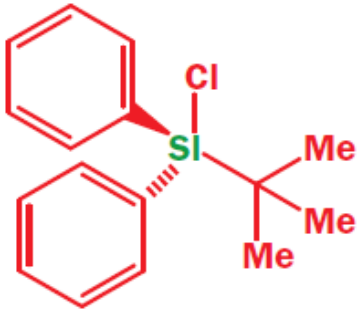
Alcohol Protecting Groups – Silyl ether



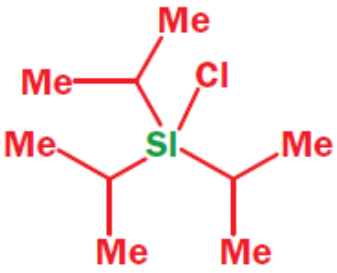
Me_3SiCl
TMSCl



***t*-$BuMe_2SiCl$**
TBDMSCl



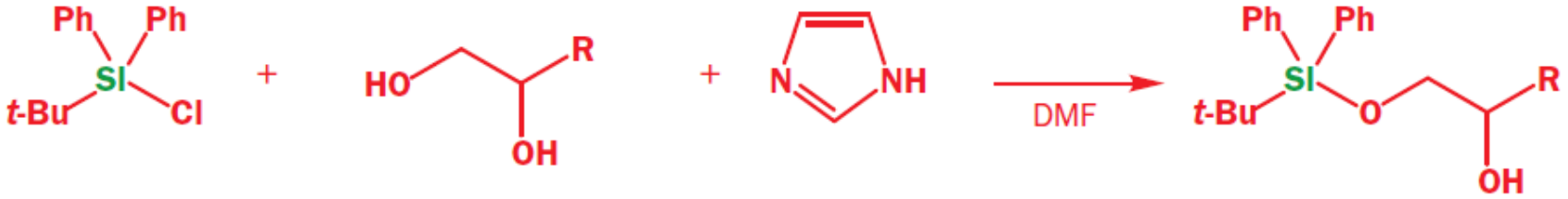
***t*-$BuPh_2SiCl$**
TBDPSCl



***i*-Pr_3SiCl**
TIPSCl

Replacement of the one of the methyl groups with a much more sterically demanding tertiary butyl group gives the TBDMS group, which is **stable to aqueous work-up or column chromatography**. The stability to these isolation and purification conditions has made **TBDMS** (sometimes called **TBS**) a very popular choice for organic synthesis

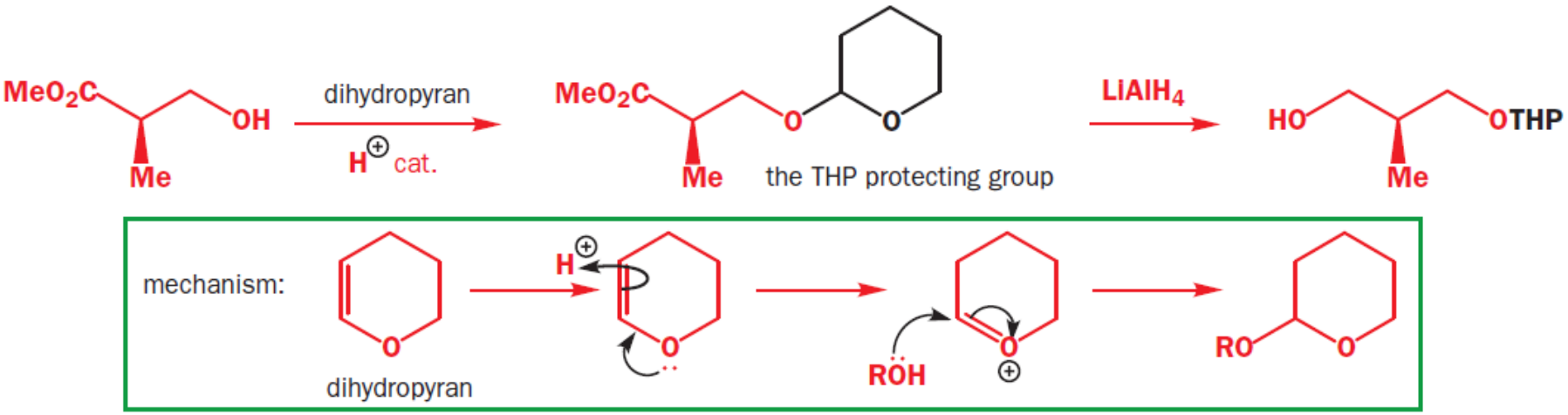
The extreme steric bulk of the TBDPS group makes it useful for **selective protection of unhindered primary alcohols** in the presence of secondary alcohols



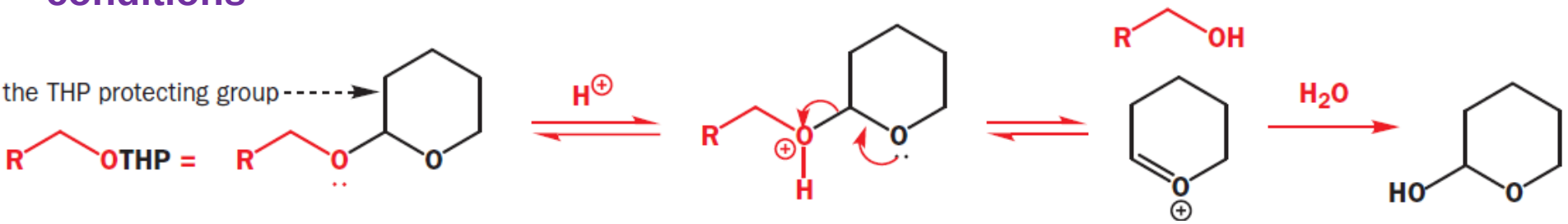
TBDPSCl diol imidazole TBDPS ether

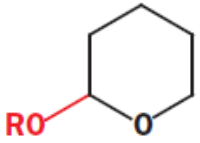
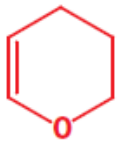
Alcohol Protecting Groups – THP

Protection: use **enol ether, dihydropyran, under acid catalysis**

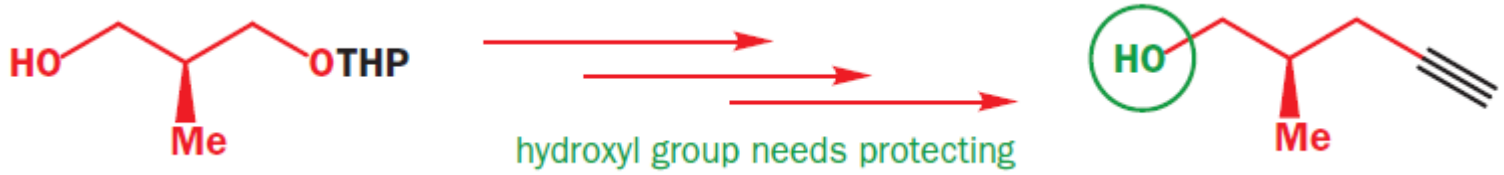


Although it is stable under **basic conditions**, the presence of the second oxygen atom makes the THP protecting group susceptible to **hydrolysis under acidic conditions**

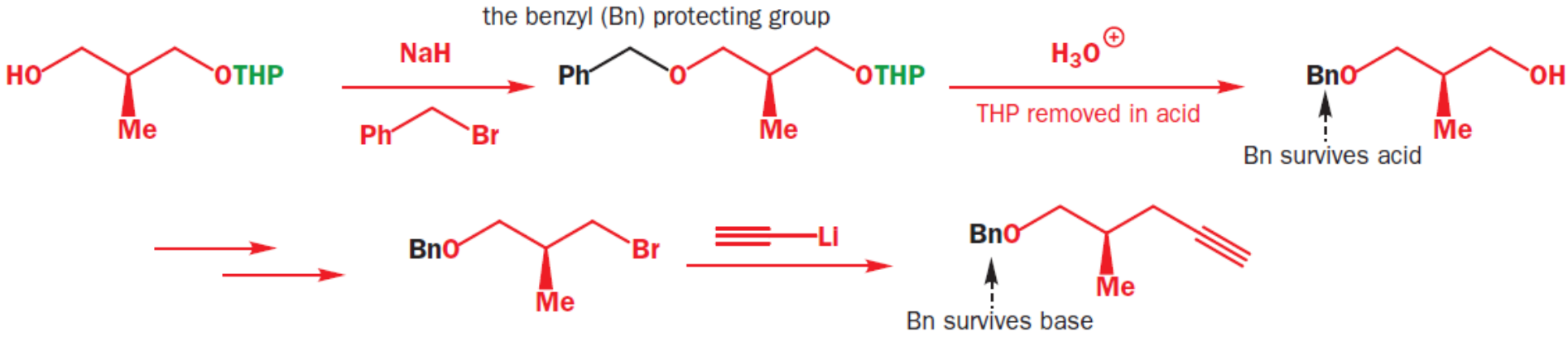


Protecting group	Structure	Protects	From	Protection	Deprotection
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro-pyran and acid	H^+, H_2O

Alcohol Protecting Groups – Benzyl ether



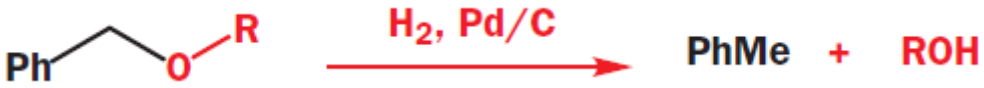
The other hydroxyl group will need protecting; the protecting group needs to **withstand the acidic conditions needed to remove the THP** protecting group (silyl ethers are not suitable); use **benzyl ether**



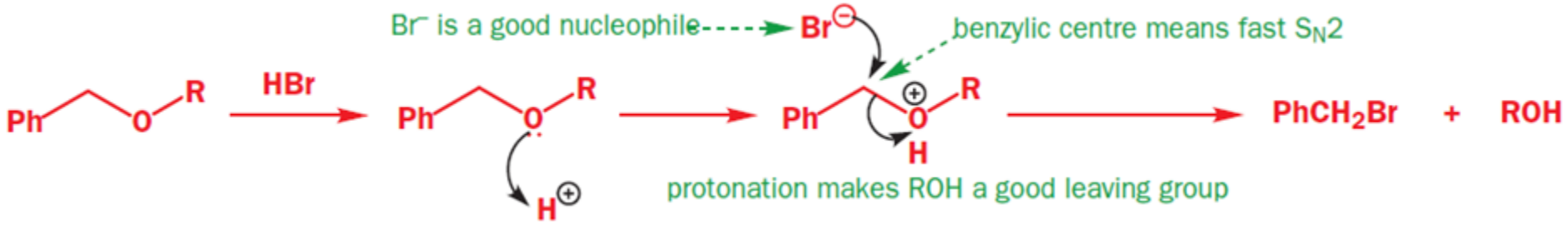
Benzyl (Bn) protecting groups are put on using **strong base** (usually sodium hydride) plus **benzyl bromide**, and are **stable to both acid and base**

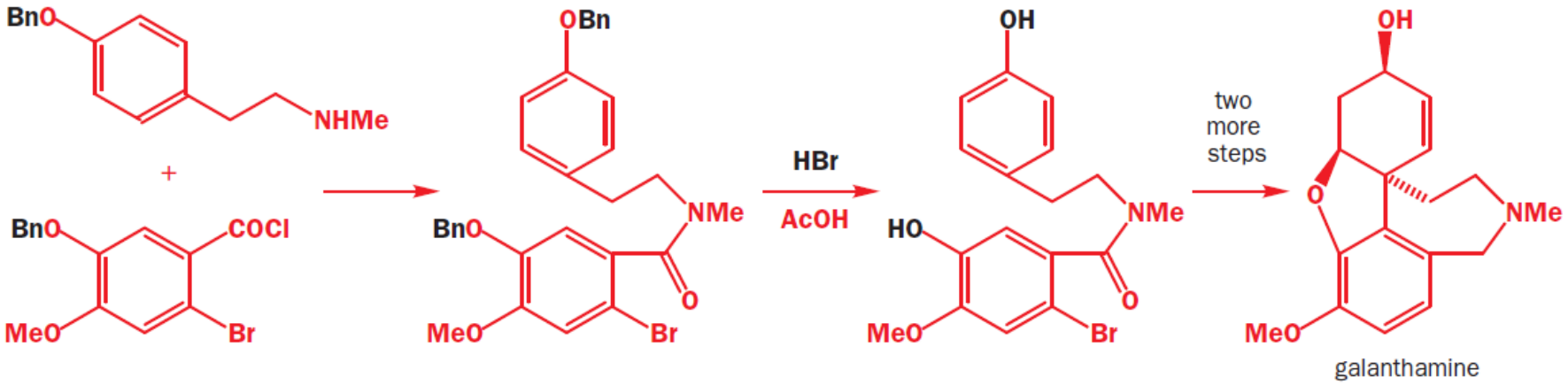
Alcohol Protecting Groups – Benzyl ether

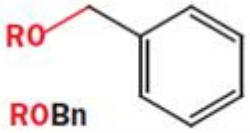
Deprotection #1: hydrogenation (hydrogenolysis) over a palladium catalyst



Deprotection #2: acid with a nucleophilic conjugate base, such as HBr





Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr

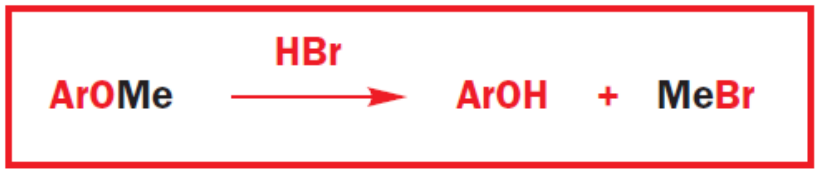
Phenol Protecting Groups – Methyl ether

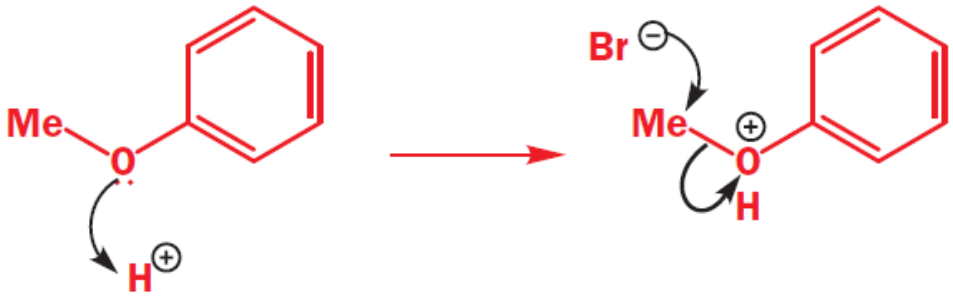
Why can't we just use a **simple alkyl ether** to protect a hydroxyl group?

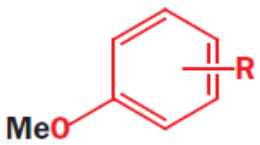
There is no problem making the ether, and it will survive most reactions—but there *is* a problem **getting an ether off** again. This is always a consideration in protecting group chemistry—you want a group that is stable to the conditions of whatever reaction you are going to do (in these examples, strong bases and nucleophiles), but **can then be removed under mild conditions that do not result in total decomposition of a sensitive molecule**

One exception: if the OH is **phenolic**; **ArOH is an even better leaving group** than ROH, so HBr will take off methyl groups from aryl methyl ethers too.

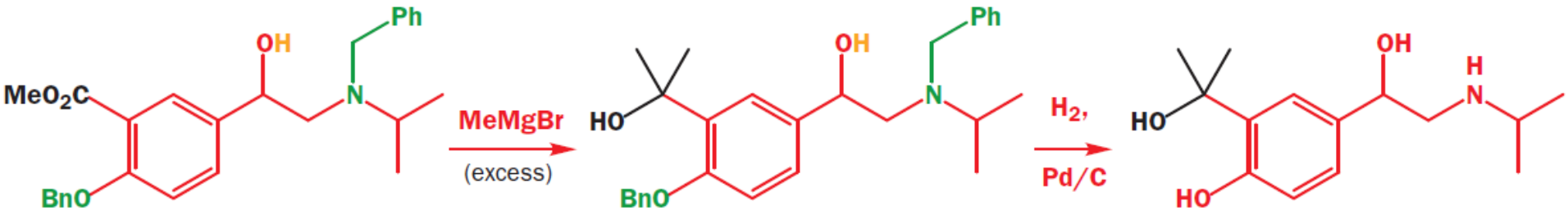
deprotection of aryl methyl ethers



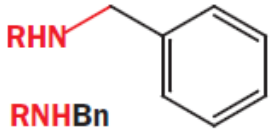


Protecting group	Structure	Protects	From	Protection	Deprotection
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI

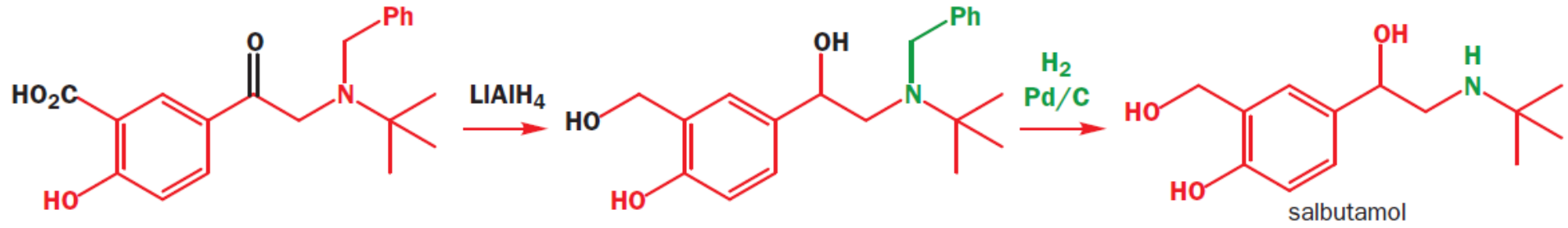
Amine Protecting Groups – Benzyl amine



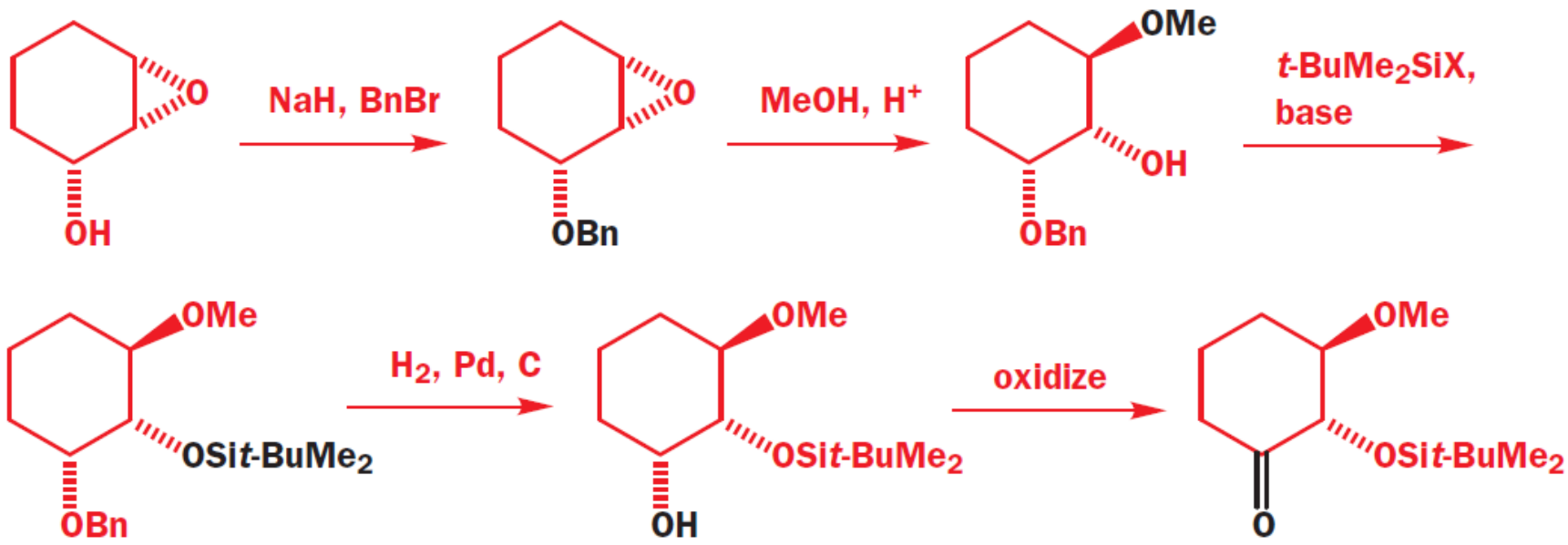
Benzyl groups are one way of **protecting secondary amines against strong bases** that might deprotonate them. However, it is the **nucleophilicity** of amines that usually poses problems of chemoselectivity, rather than the acidity of their NH groups

Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl amine (NBn)		amines	strong bases	BnBr, K_2CO_3	H_2, Pd

Example:

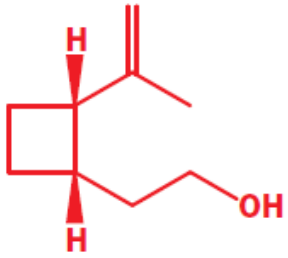


Protecting Groups – Examples

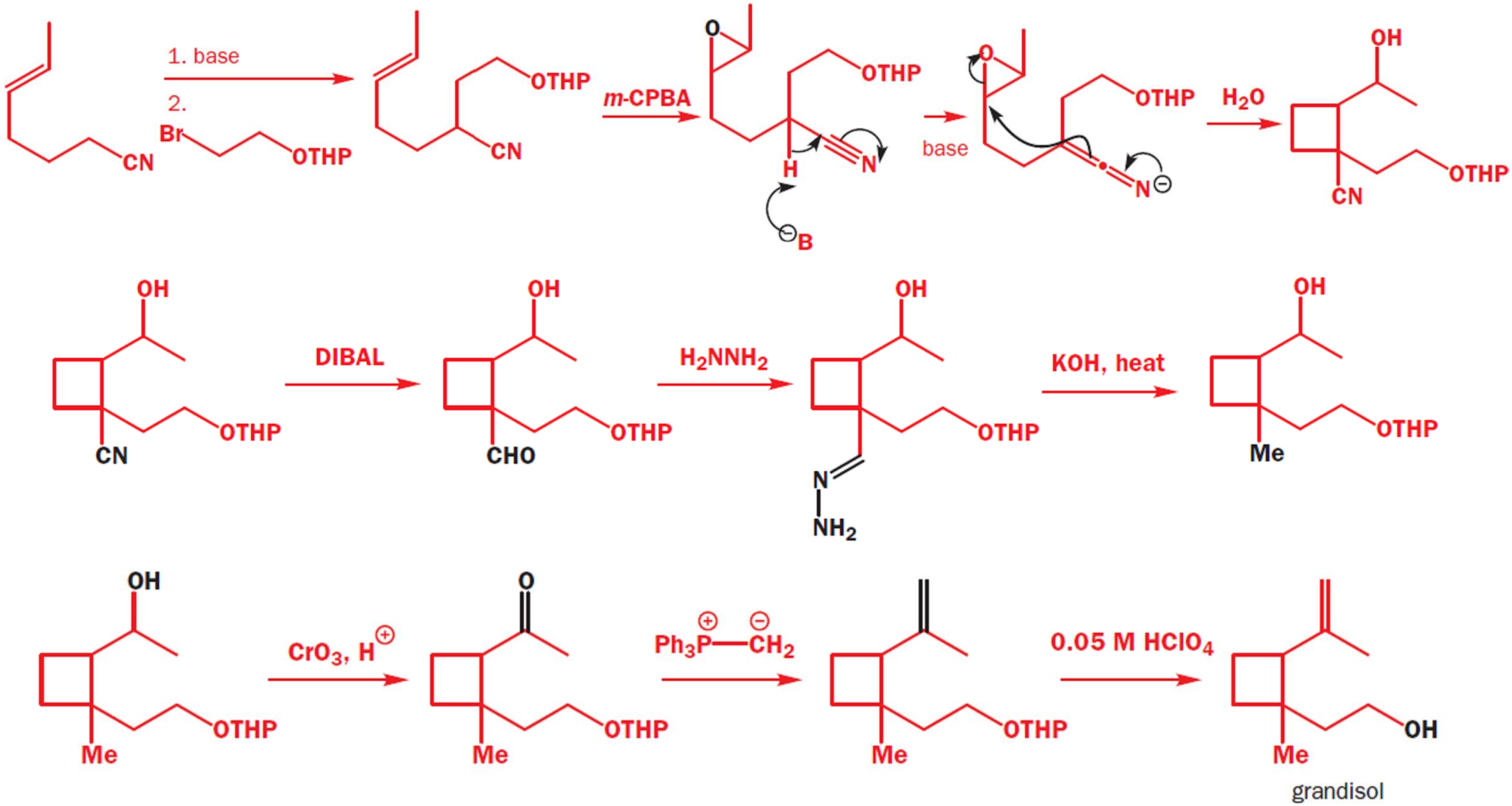


Synthesis of Grandisol

House-flies are irritating and a minor health hazard, but the cotton boll weevil is an enormously destructive pest of the American cotton crop and is responsible for vast economic losses. The weevil has a **pheromone** called **grandisol**



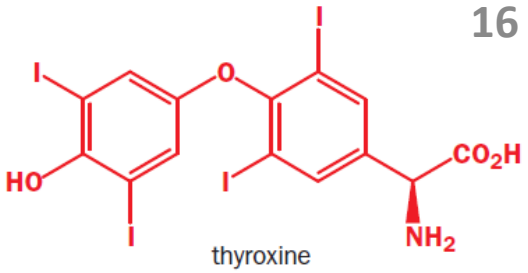
grandisol

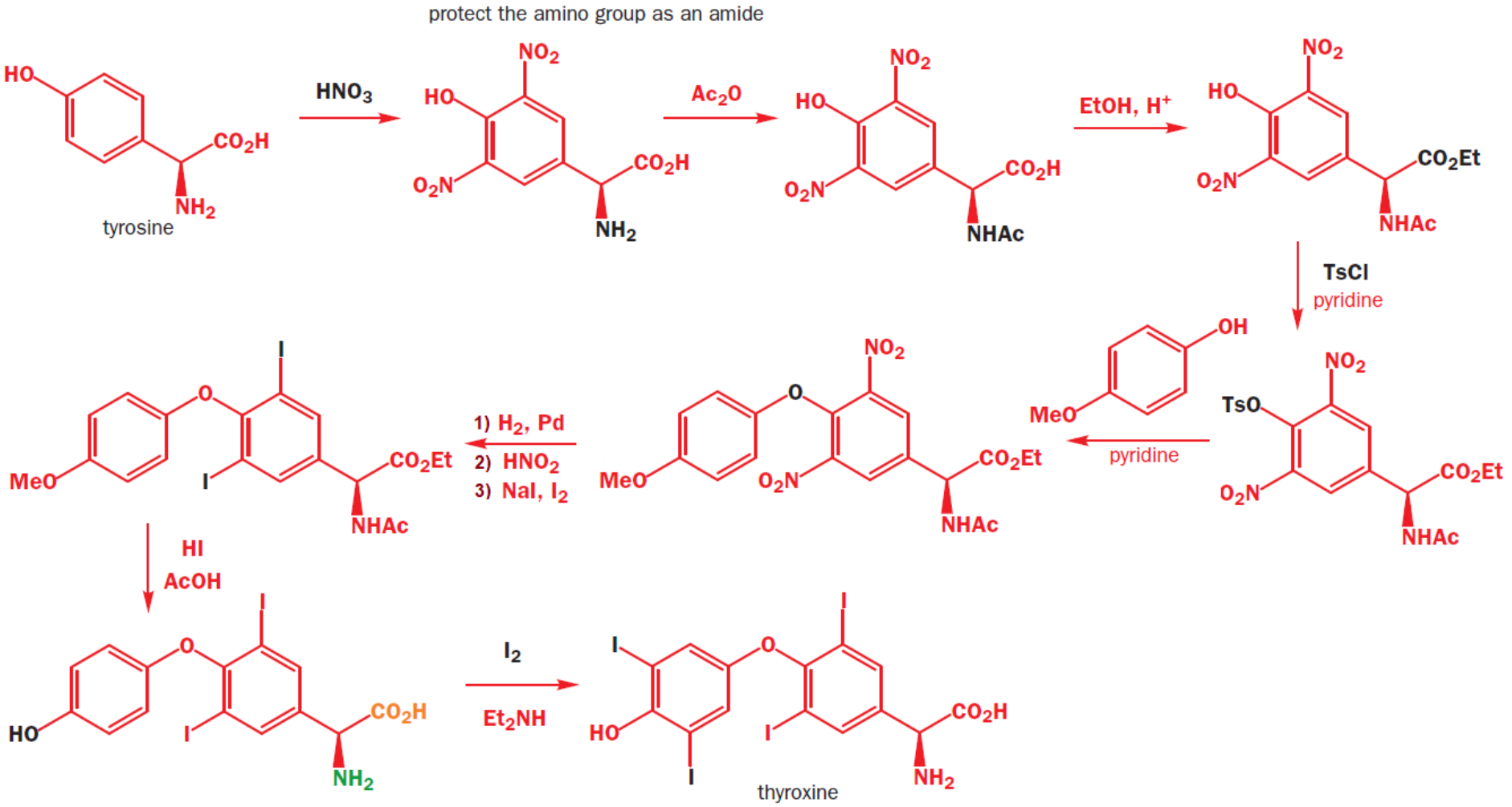


grandisol

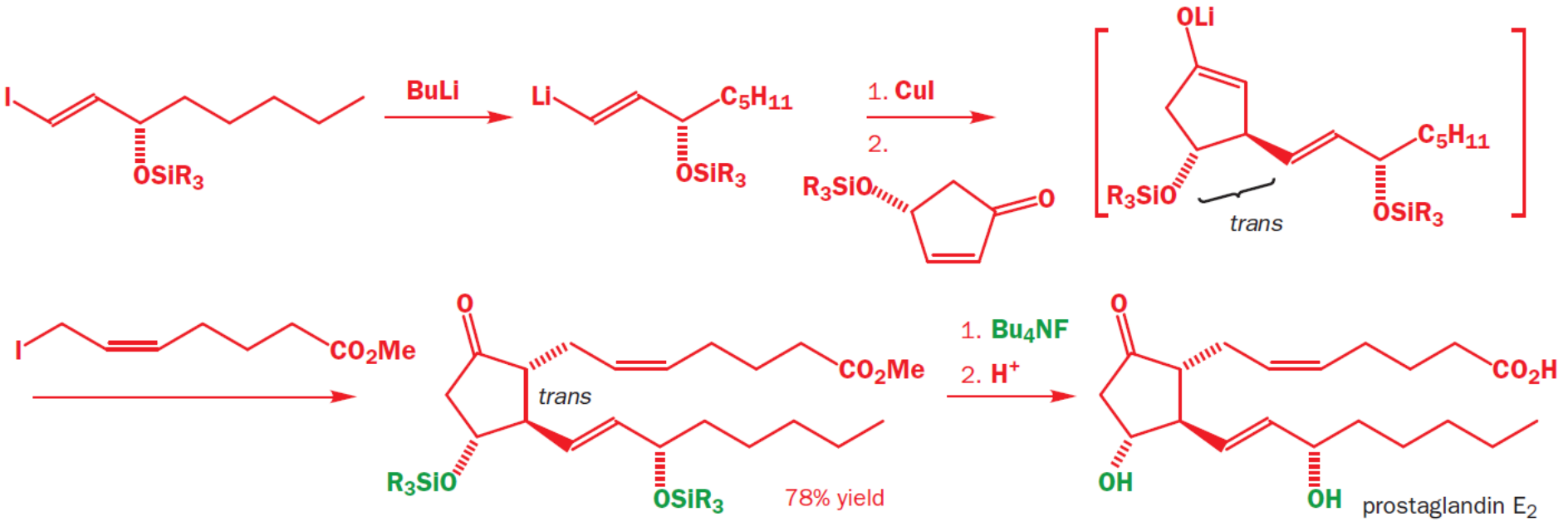
Synthesis of Thyroxine

Thyroxine is a hormone for controlling metabolic rate. Lack of thyroxine (or rather, of the iodine needed to make it) causes goitre

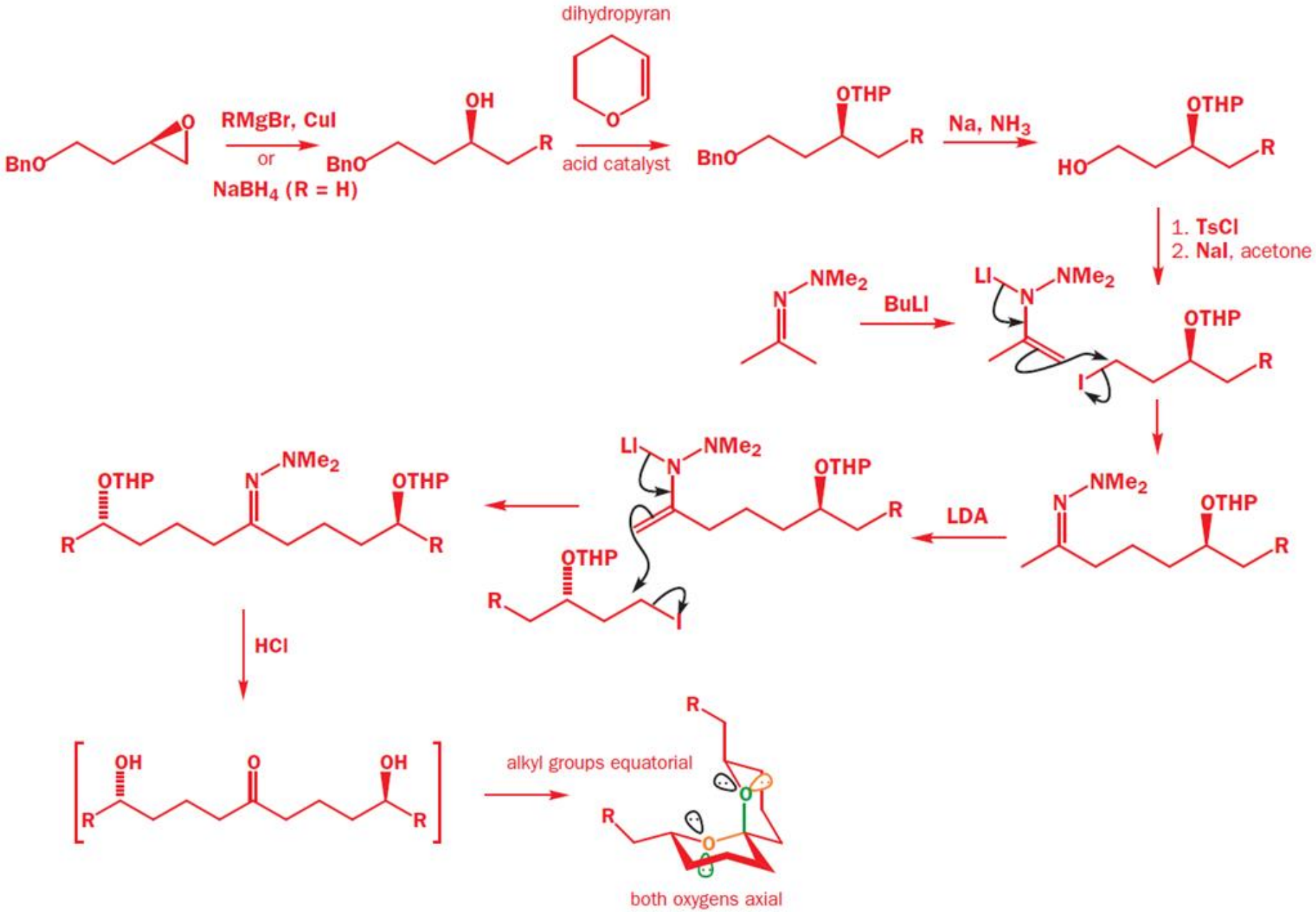




Protecting group in synthesis

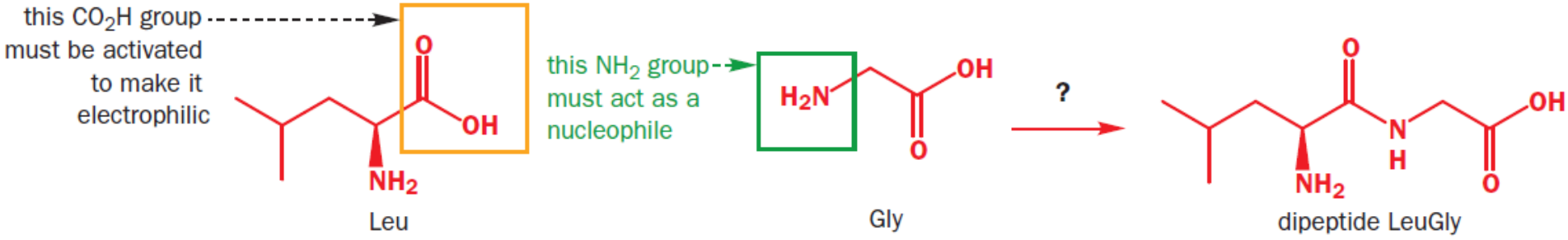


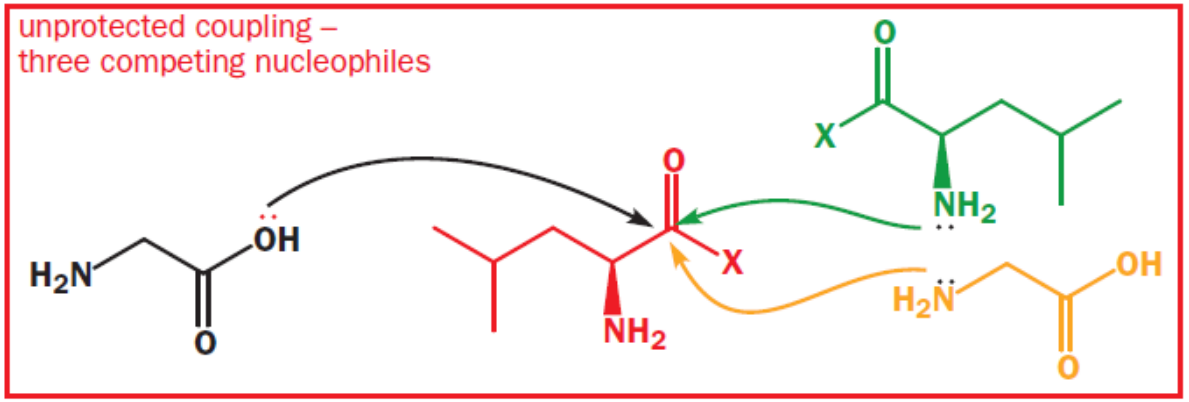
Protecting group in synthesis



Peptide synthesis

The ability to control the reactivity of **amines** and **carboxylic acids** is vital to the controlled synthesis of peptides





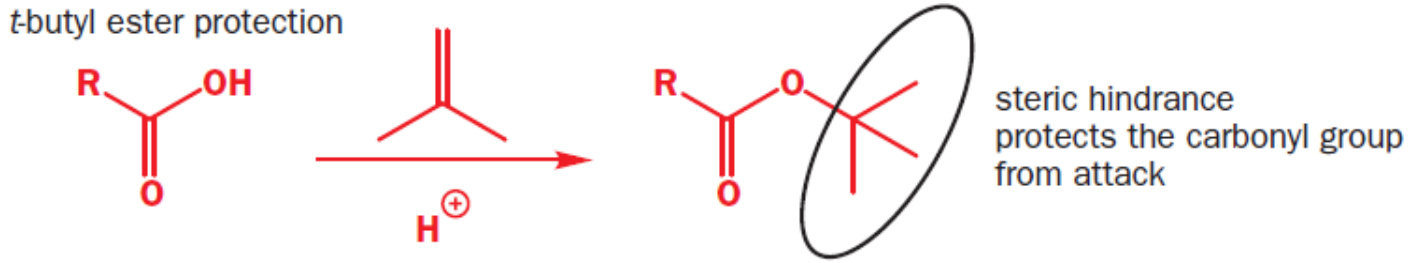
We need to protect both the **NH_2 group of leucine** and the **CO_2H group of glycine**

There is no point using an **amide** to protect the amine since we would have great difficulty hydrolysing the amide in the presence of the amide bond we are trying to form

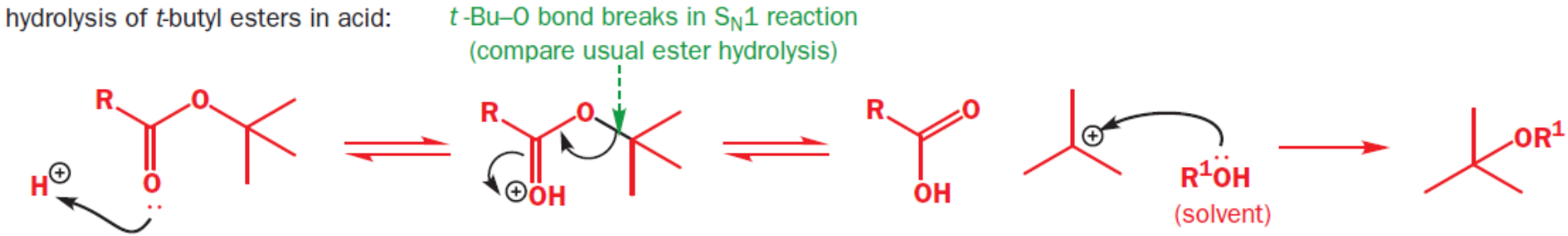
Carboxylic Protecting Groups – *t*-butyl ester

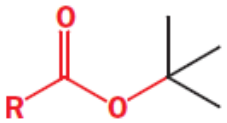
Making an ester is the obvious way to stop CO_2H groups interfering as acids or as nucleophiles. However, **simple methyl and ethyl esters may pose problems**—they can **still react with such nucleophiles as amines**

Steric bulk means that ***t*-butyl esters** are **resistant to nucleophilic attack** at the carbonyl group, and that includes hydrolysis under basic conditions (nucleophilic attack by HO^-). But they do **hydrolyse relatively easily in acid**



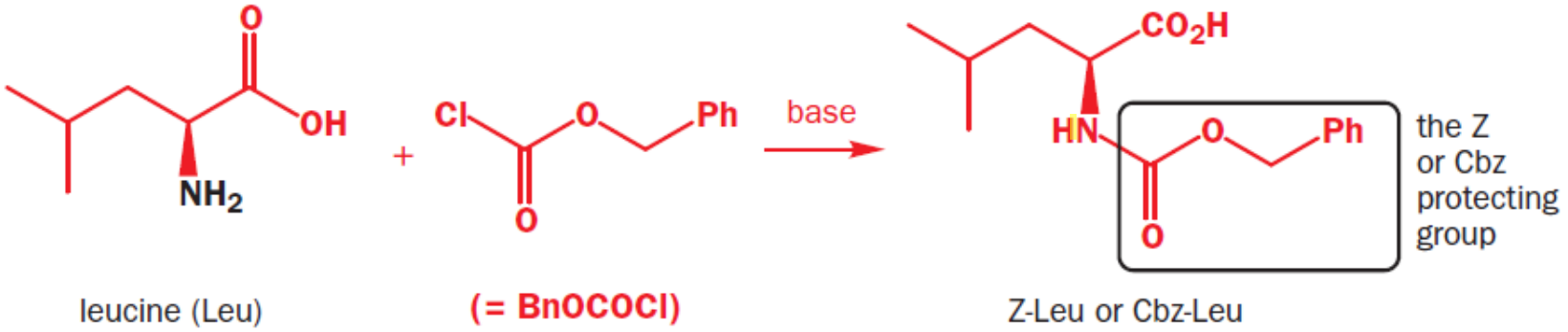
The hydrolysis does not involve nucleophilic attack at carbonyl; it is **SN_1 of *t*-Bu**



Protecting group	Structure	Protects	From	Protection	Deprotection
***t*-butyl ester** (CO_2Bu-*t*)		carboxylic acid (RCO_2H)	bases, nucleophiles	isobutene, H^+	H_3O^+

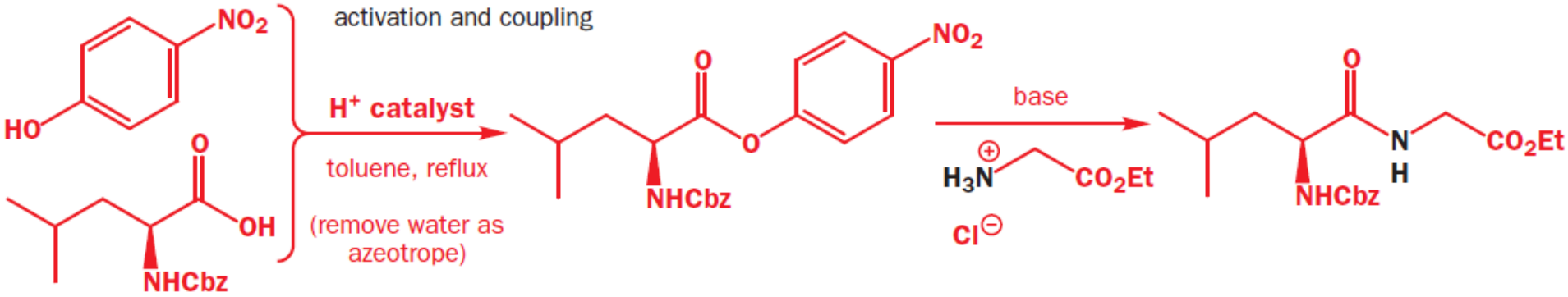
Amine Protecting Groups – Z or Cbz

Cbz (Z) are put on by treating with **benzyl chloroformate** (BnOCOCl) and **weak base**



leucine (Leu) (= BnOCOCl) Z-Leu or Cbz-Leu

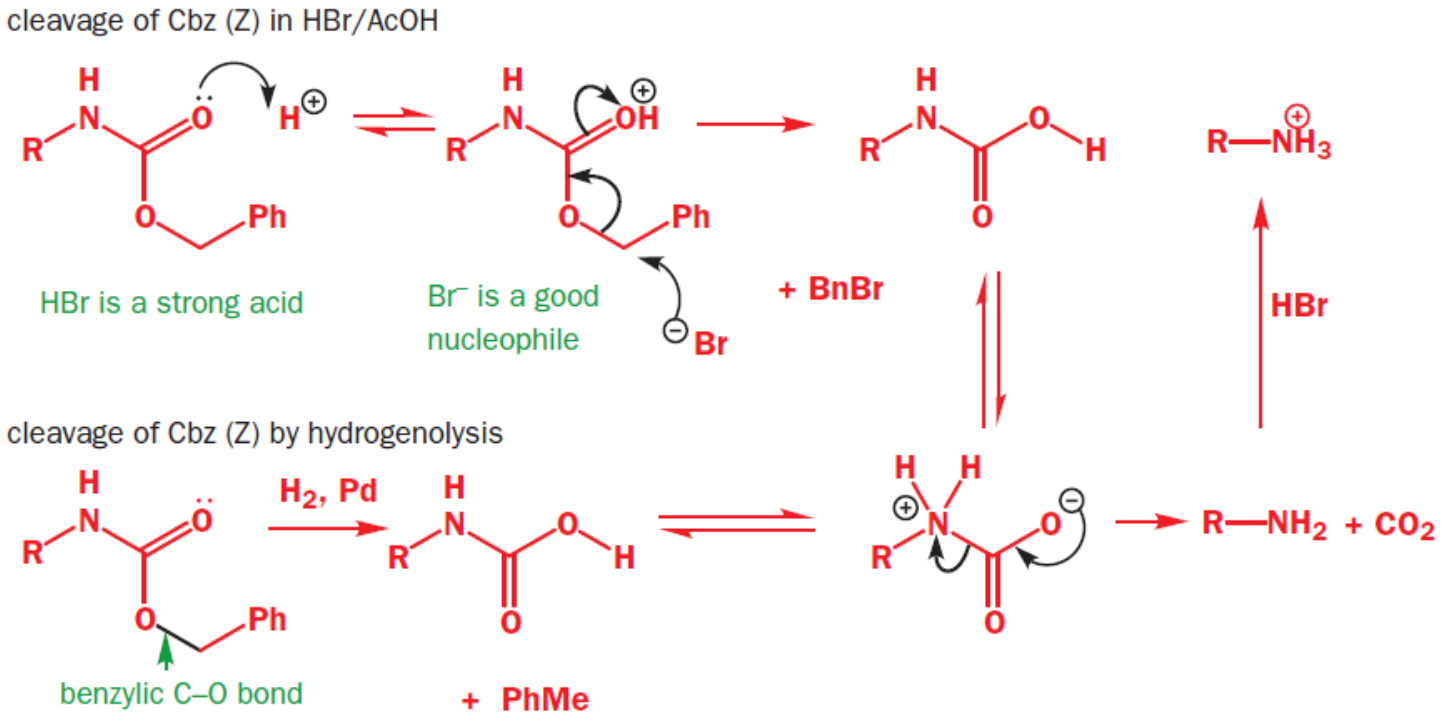
Cbz-protected amines behave like amides; they are **no longer nucleophilic**, because the nitrogen's lone pair is tied up in conjugation with the carbonyl group. They are **resistant to both aqueous acid and aqueous base**

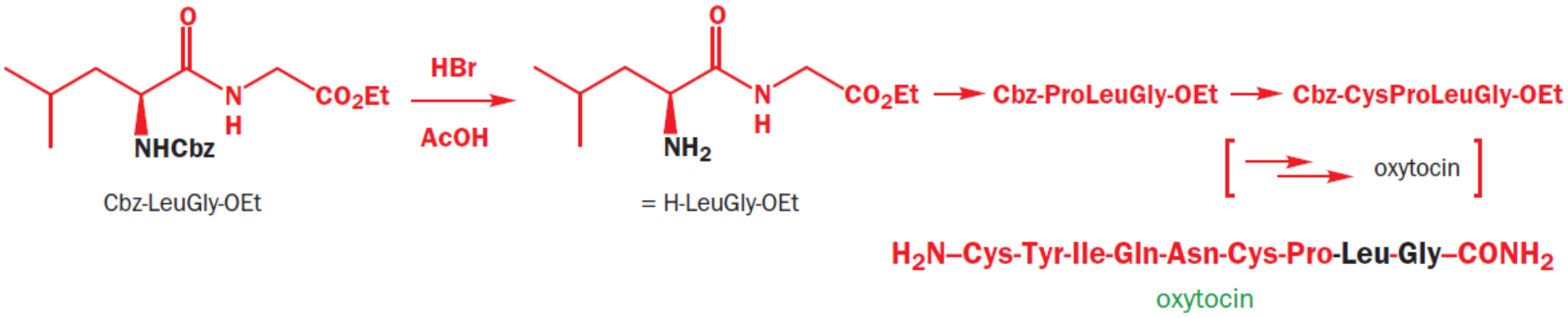


The Cbz-protected leucine next had to be **activated** so that it would react with the glycine. **Phenoxide**, especially when substituted with electron withdrawing substituents, is a good leaving group

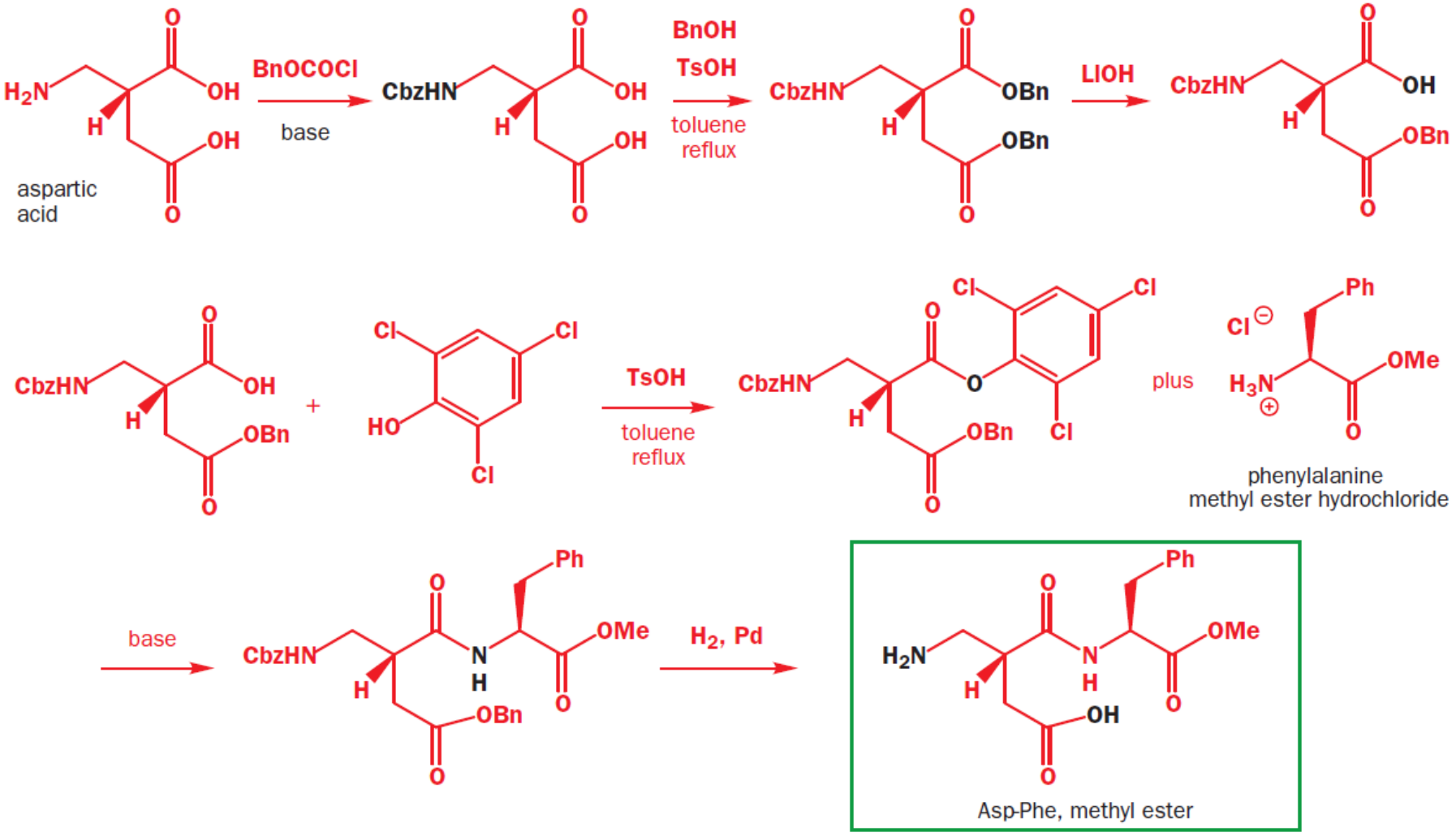
Amine Protecting Groups – Z or Cbz

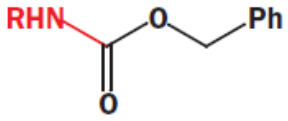
Deprotection: HBr or hydrogenolysis



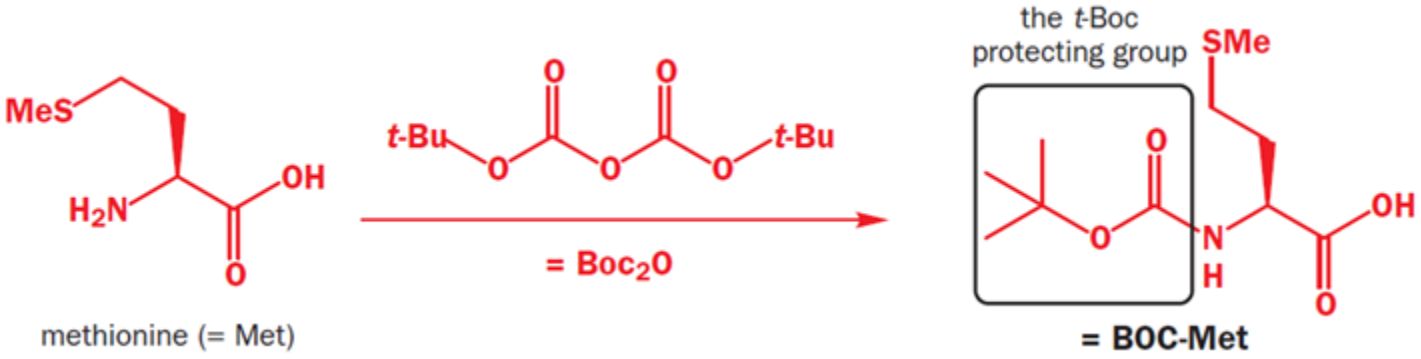


Amine Protecting Groups – Z or Cbz

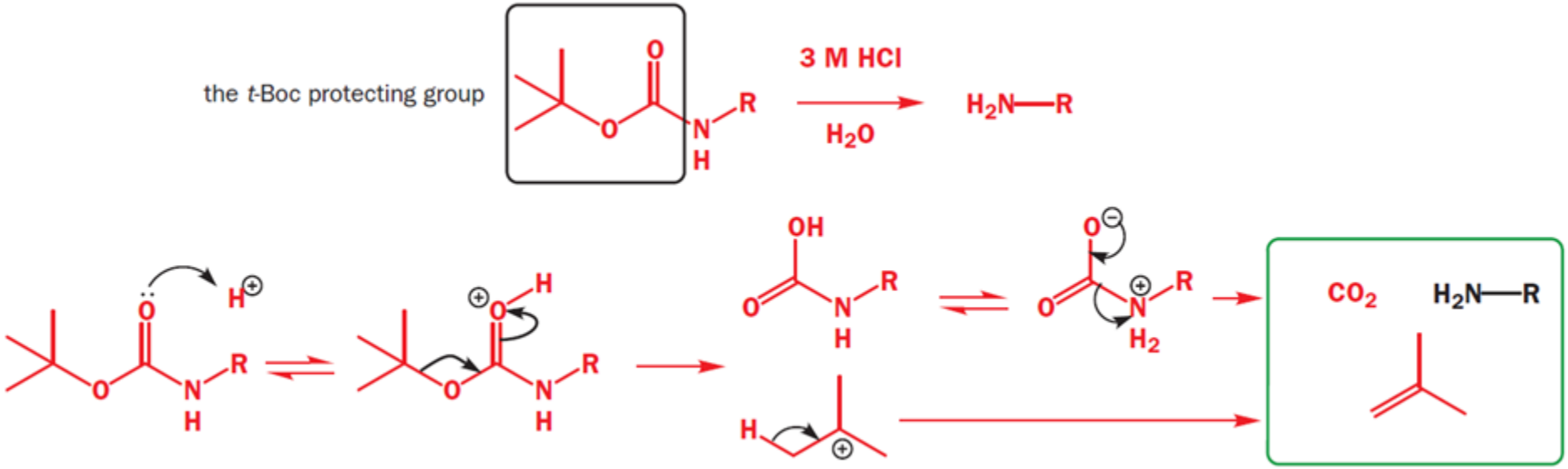


Protecting group	Structure	Protects	From	Protection	Deprotection
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH or H_2, Pd

Amine Protecting Groups – Boc

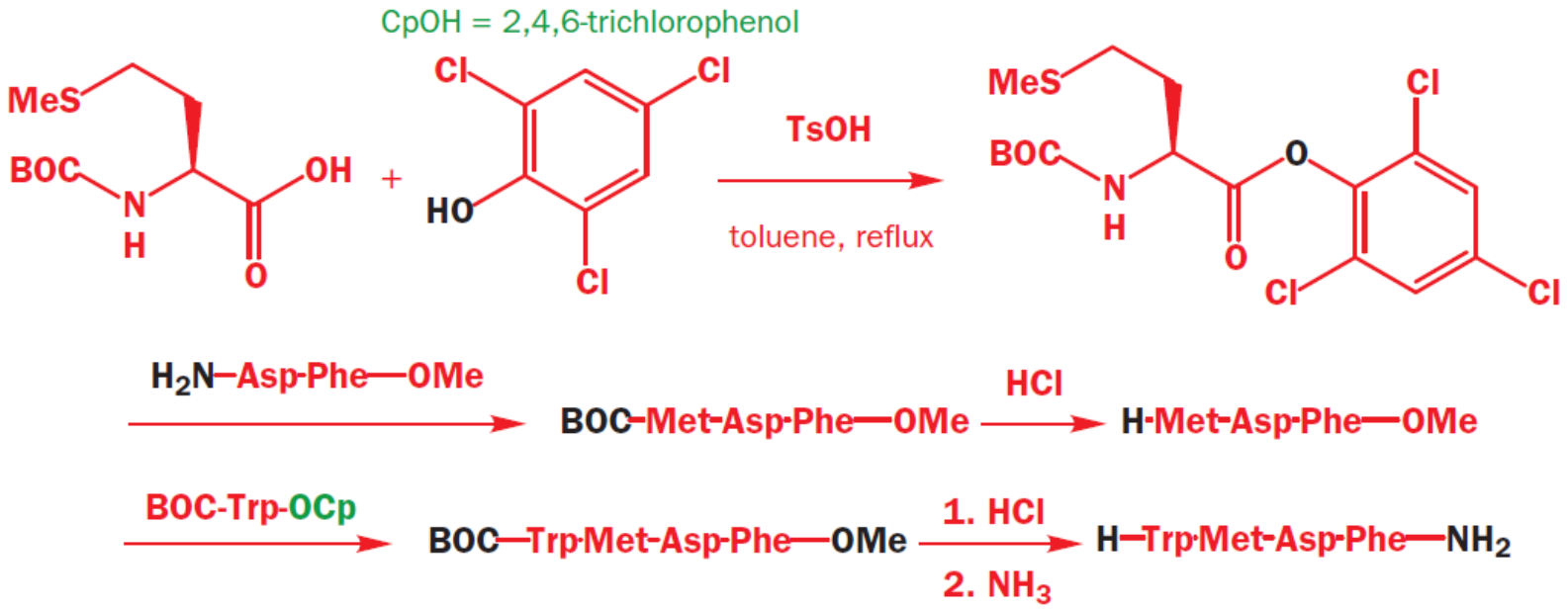


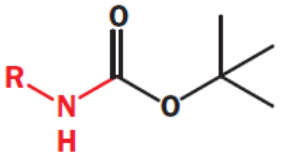
Like Cbz, the Boc group is **resistant to basic hydrolysis**. But, unlike Cbz, it can be removed simply with **dilute aqueous acid**. Just 3M HCl will hydrolyse it



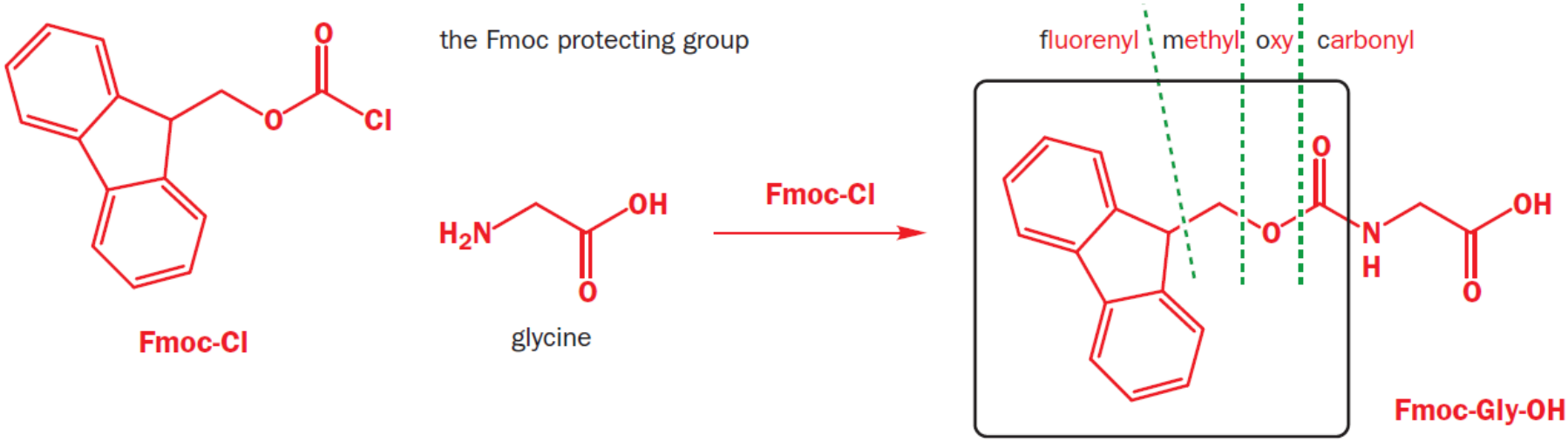
Amine Protecting Groups – Boc

Methionine (Met) has been BOC-protected, and is ready for activation—as a 2,4,6-trichlorophenyl ester (Cp) this time and coupling with the deprotected Asp-Phe-OMe. Aqueous acid takes off the BOC group without hydrolysing peptide or ester bonds, and a repeat of this cycle with BOC-tryptophan trichlorophenyl ester (BOC-Trp-OCp) finally gives the tetrapeptide



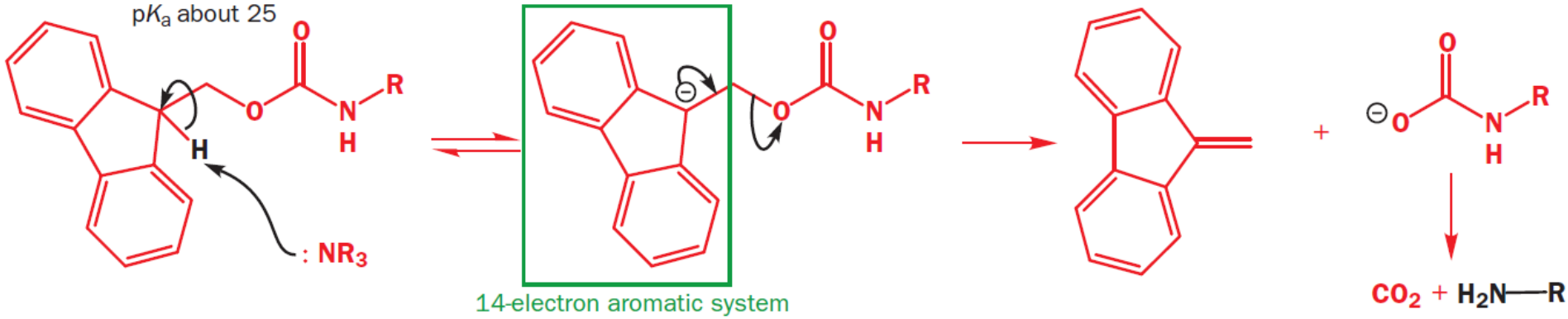
Protecting group	Structure	Protects	From	Protection	Deprotection
***t*-Boc** (OCOBu-*t*)		amines	electrophiles	$(t\text{-BuOCO})_2O$, base	H^+, H_2O

Amine Protecting Groups – Fmoc

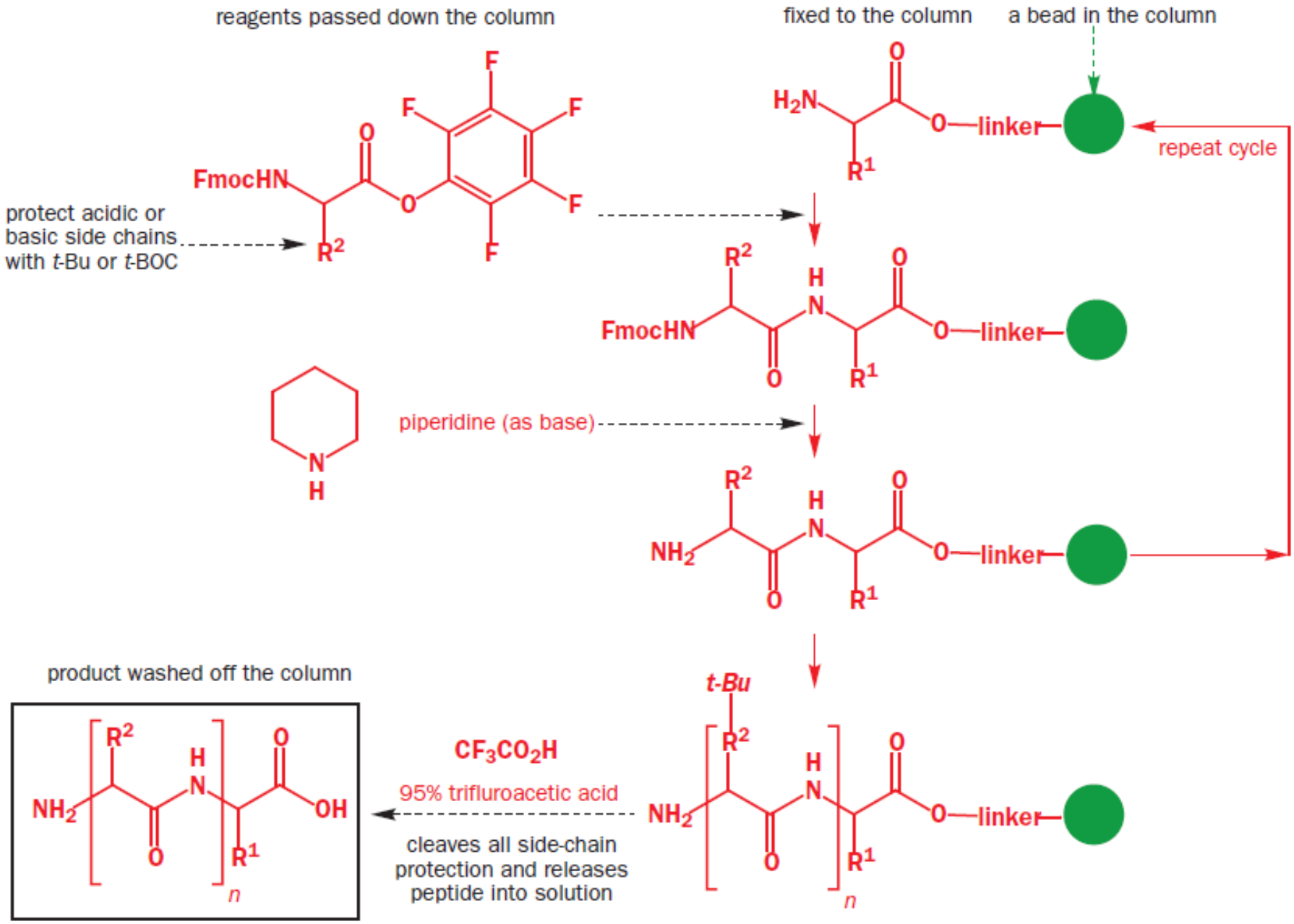


Fmoc has a susceptibility **inverse** to that of Boc. It cannot be lost by substitution in the manner of Cbz or Boc because neither SN1 nor SN2 mechanisms can operate at the ringed hindered carbon atom; it is **stable to acid**

It has a rather **acidic proton** (pKa about 25), shown in black. Treatment of Fmoc protected amines with **base eliminates a fulvene** to reveal the NH_2 group



Solid-phase peptide synthesis 1



Solid-phase peptide synthesis 1

The synthesis of peptides on a **solid support** has become extremely important, because it allows peptides to be synthesized by machines

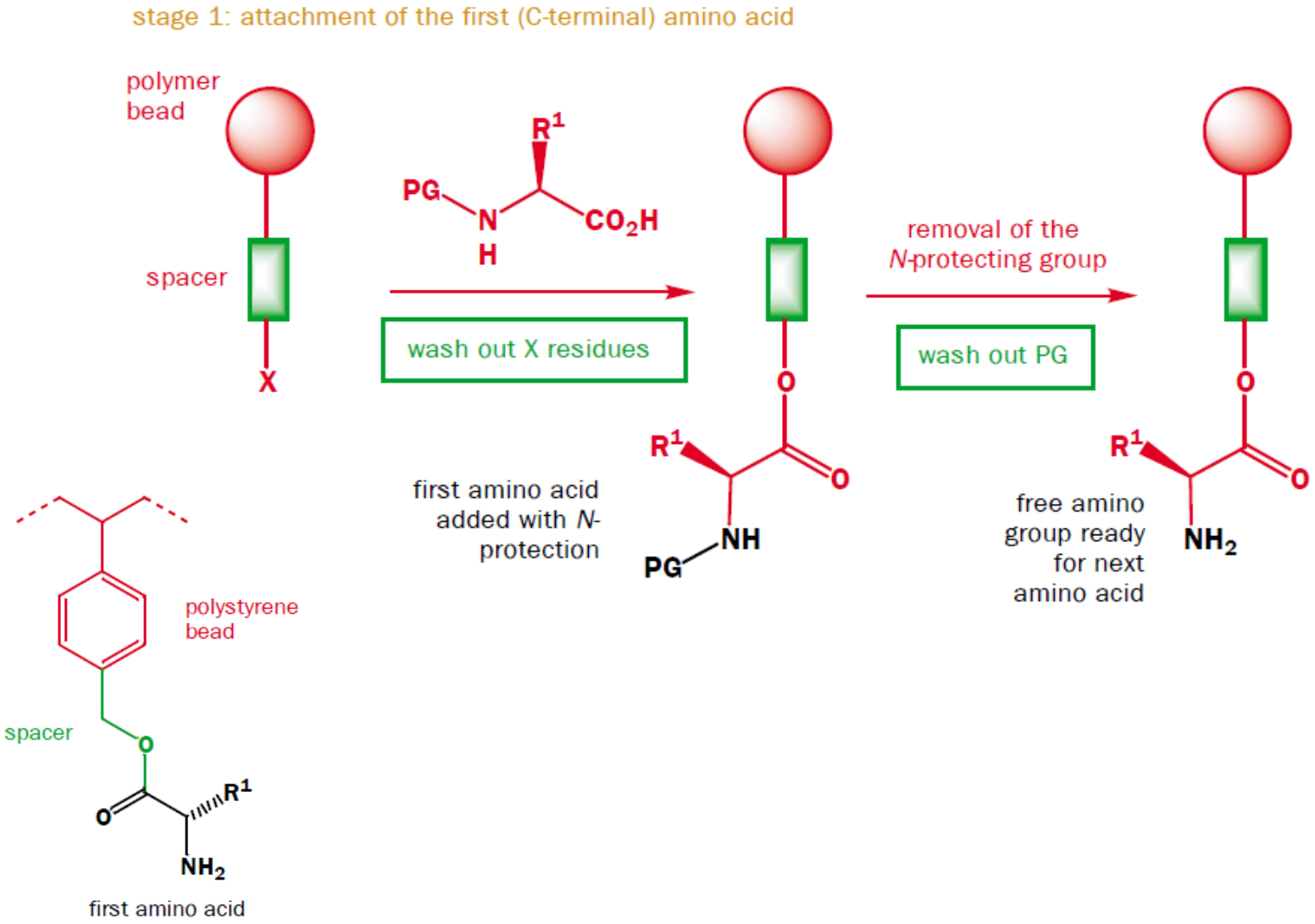
The idea is that the ***C*-terminus amino acid is tethered to the resin** by means of a **carbamate linker** that is **stable to mild acid or base**. The peptide chain is then built up and, when complete, is released by cleaving the linker with **strong acid**

The **side chains** of the amino acids in this approach are also protected with **acid-labile** groups (*t*-butyl esters and BOC, for example), so that they too are revealed only in the final deprotection step

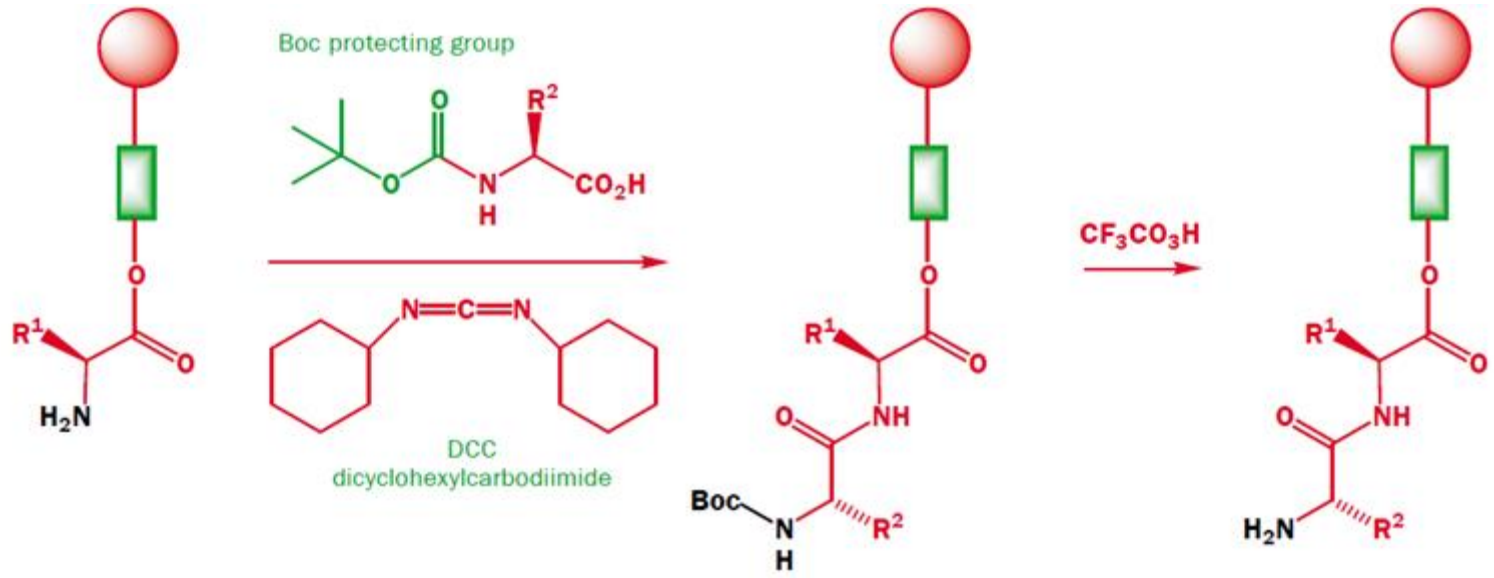
Acid cannot therefore be used for protection for the *N*-terminus of the chain as it grows, so the solution is to use Fmoc. Each amino acid is introduced as its **Fmoc-protected pentafluorophenyl ester**, and then the Fmoc group is **cleaved with piperidine** ready for the next residue to be added

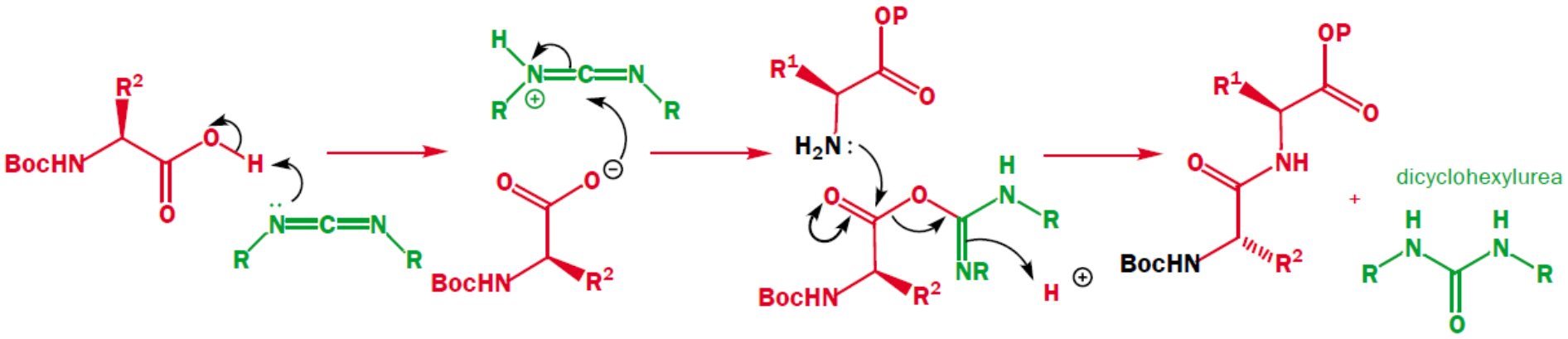
Once the first amino acid is fixed to the column, reagents are added simply by passing solutions down the column. Any excess or by-products are washed off. Finally, the product is **released by passing a solution of CF_3CO_2H down the column**

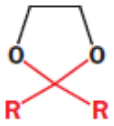
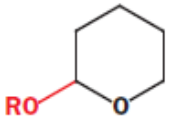
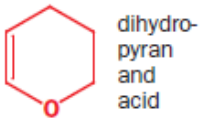
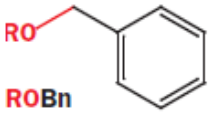
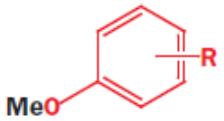
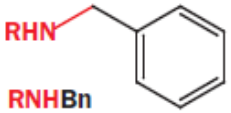
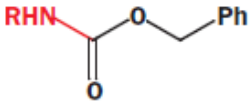
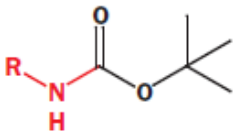
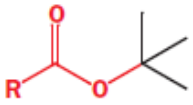
Solid-phase peptide synthesis 2



Solid-phase peptide synthesis 2

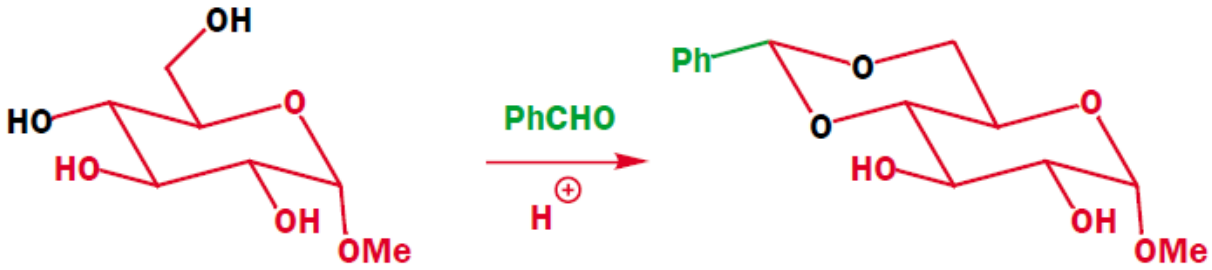




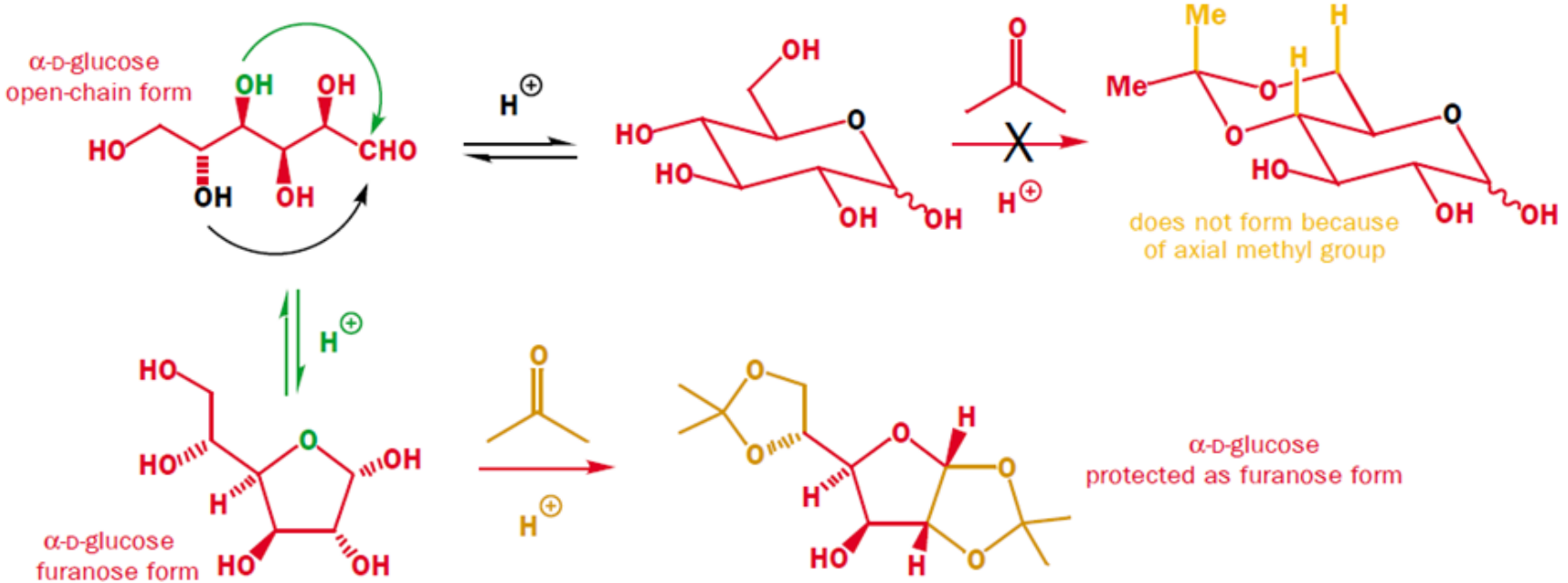
Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H^+ cat.
trialkylsilyl (R_3Si-, e.g. TBDMS)		alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro-pyran and acid	H^+, H_2O
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI
benzyl amine (NBn)		amines	strong bases	BnBr, K_2CO_3	H_2, Pd
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH, or H_2, Pd
***t*-Boc** (OCOBu-*t*)		amines	electrophiles	$(t\text{-BuOCO})_2O$, base	H^+, H_2O
Fmoc fluoroenyloxycarbonyl	see text	amines	electrophiles,	Fmoc-Cl	base, e.g. amine
***t*-butyl ester** (CO_2Bu-*t*)		carboxylic acid (RCO_2H)	bases, nucleophiles	isobutene, H^+	H_3O^+

Protecting group in sugar chemistry

When benzaldehyde is used, it chose the only pair to give a **six-membered ring** which is **trans-fused** on the old so that a beautifully stable **all-chair** bicyclic structure results, with the **phenyl group in an equatorial position** in the new chair acetal ring

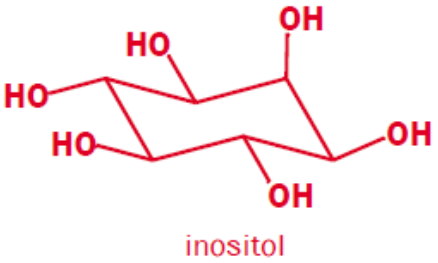


Acetals formed from acetone have a quite different selectivity, it prefer to be **five**- rather than six-membered rings to avoid **axial interactions**



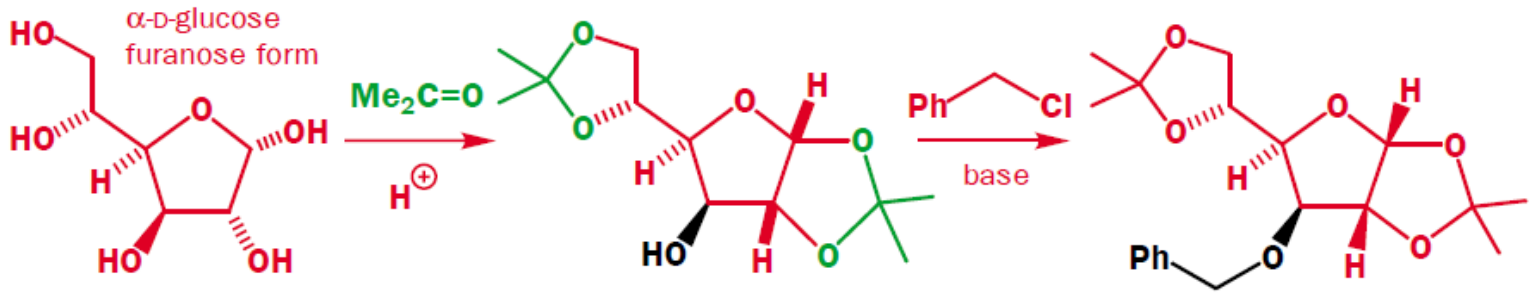
Synthesis of inositols

Inositol controls many aspects of our chemistry that require **communication between the inside and the outside of a cell**. Inositol-1,4,5-triphosphate (IP3) can open calcium channels in cell membranes to allow calcium ions to escape from the cell

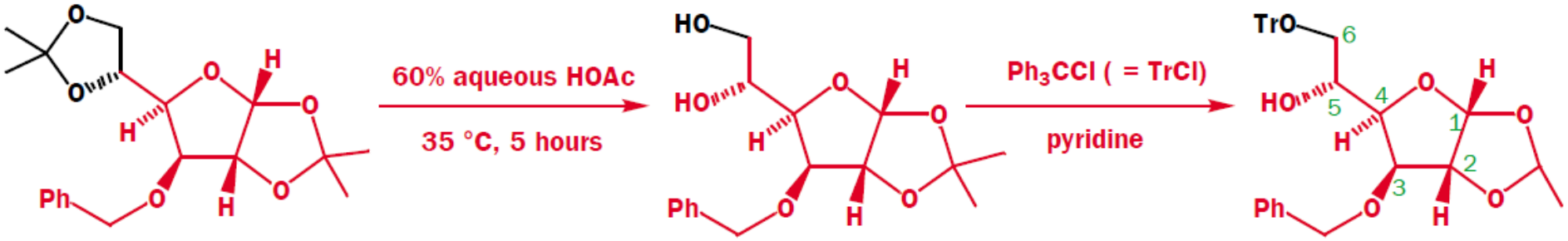


inositol

The synthesis starts with glucose trapped in its furanose form by a **double acetone acetal**. The one remaining OH group is first blocked as a **benzyl ether**

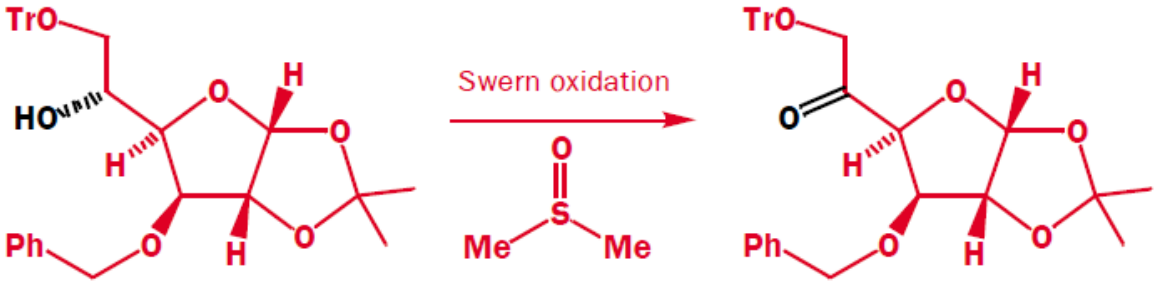


Next, one of the acetals is hydrolysed under very mild conditions, and the primary alcohol is protected as a **trityl ether**. This is an S_N1 reaction with an **enormous electrophile**—so big that it goes on **primary alcohols only**

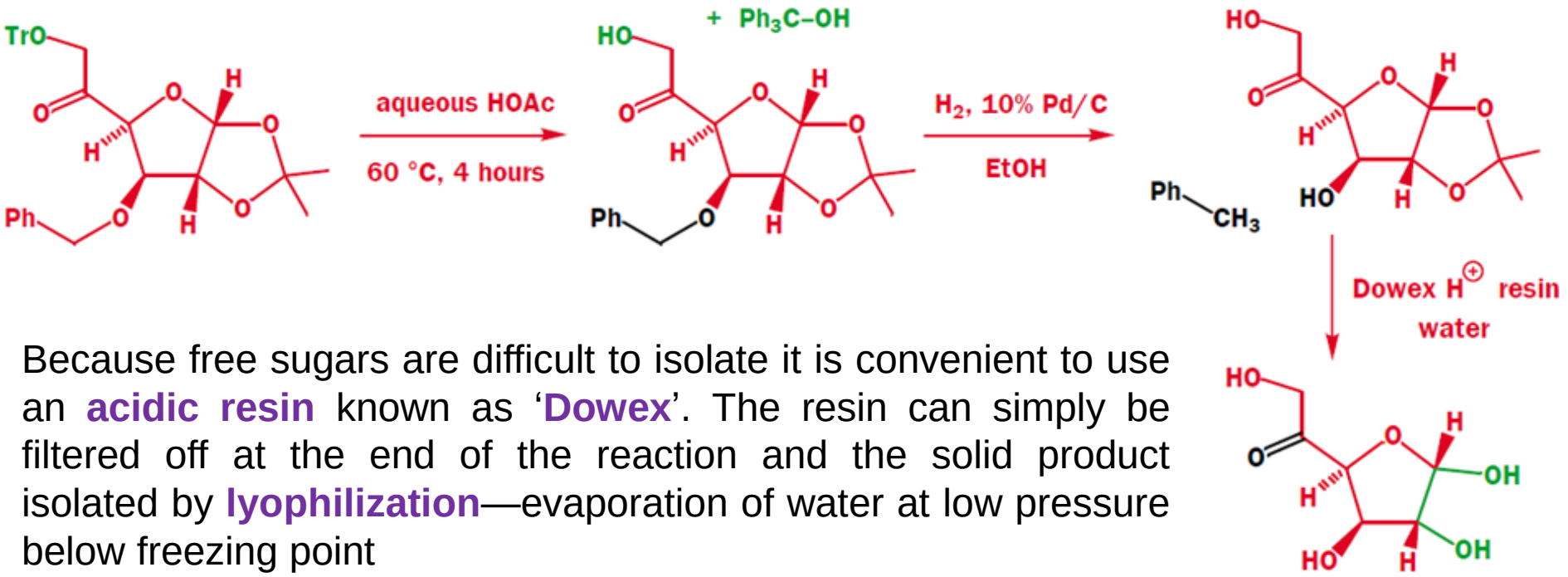


Synthesis of inositols

Only the OH at C5 is free: it can now be oxidized using a Swern procedure



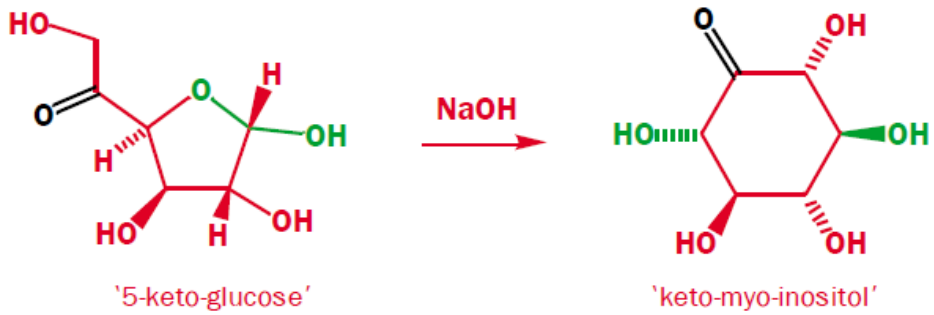
Deprotections:

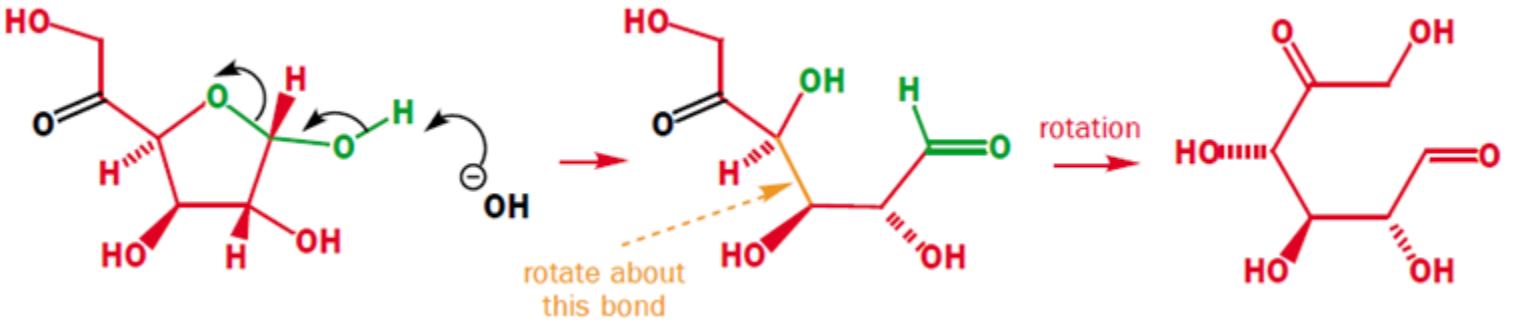


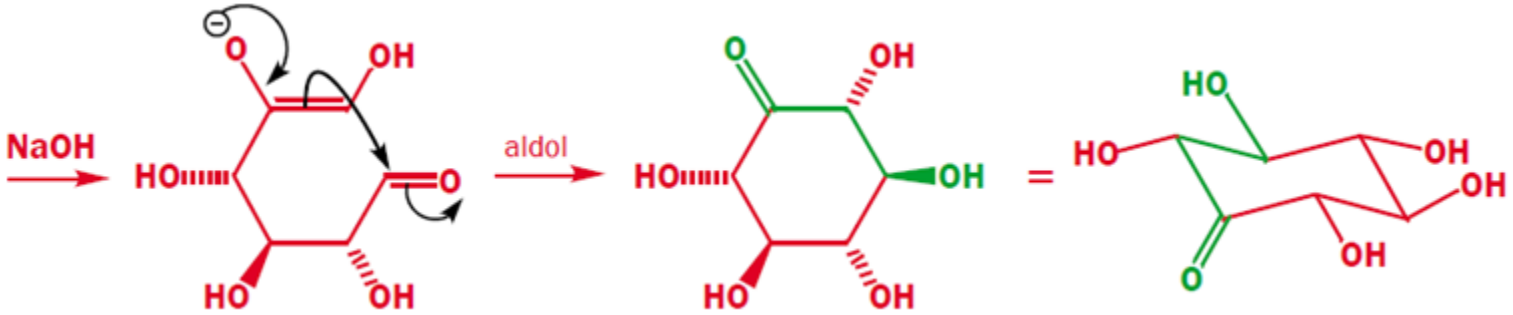
Because free sugars are difficult to isolate it is convenient to use an **acidic resin** known as '**Dowex**'. The resin can simply be filtered off at the end of the reaction and the solid product isolated by **lyophilization**—evaporation of water at low pressure below freezing point

Synthesis of inositols

Treatment of this free ‘glucose ketone’ with **aqueous NaOH** gives the ketone of myo-inositol as the major product together with some of the other diastereoisomers

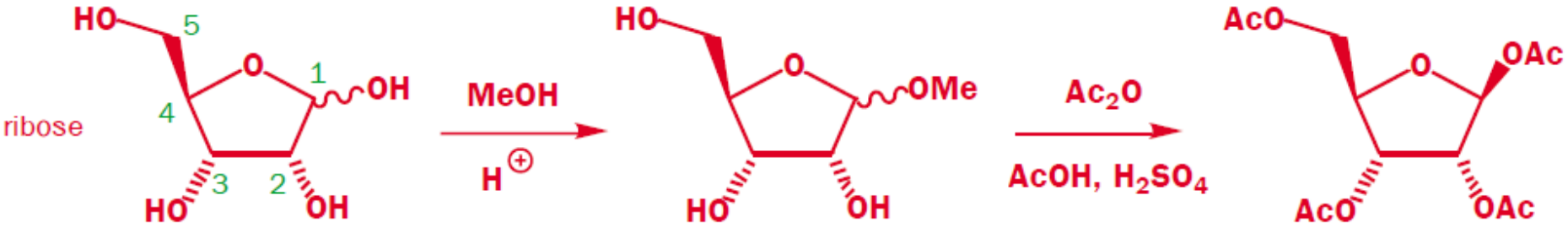




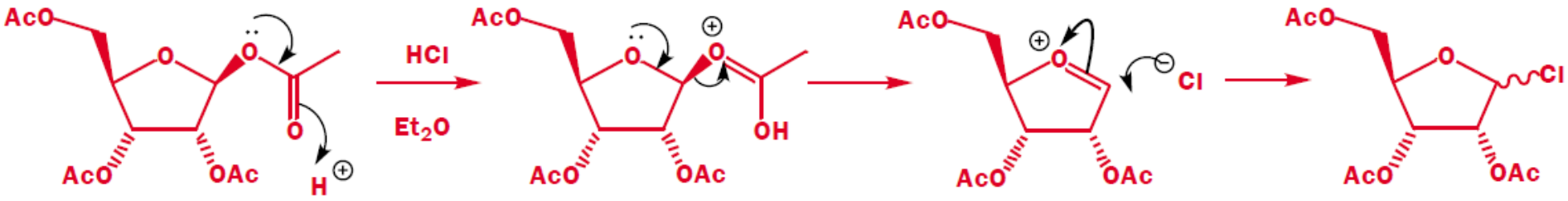


Synthesis of Nucleotide from Ribose

Since ribose is rather unstable to acetylation conditions, the **methyl glycoside** (which is formed under very mild conditions) is used



Tetraacetate can be made using acetic anhydride in acidic solution. All of the OH groups react by **nucleophilic attack** on the carbonyl group of the anhydride with retention of configuration except for the **anomeric OH, which esterifies by an S_N1** mechanism



the anomeric centre can be activated towards nucleophilic attack by replacement of acetate with chloride by S_N1 reaction

Synthesis of Nucleotide from Ribose