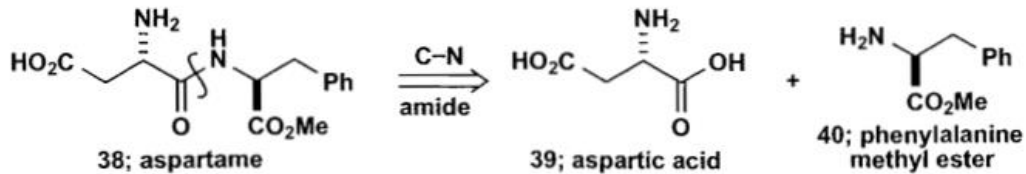
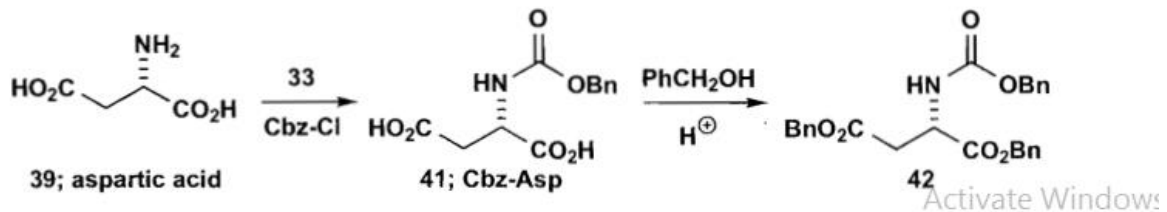


Lecture # 10-2

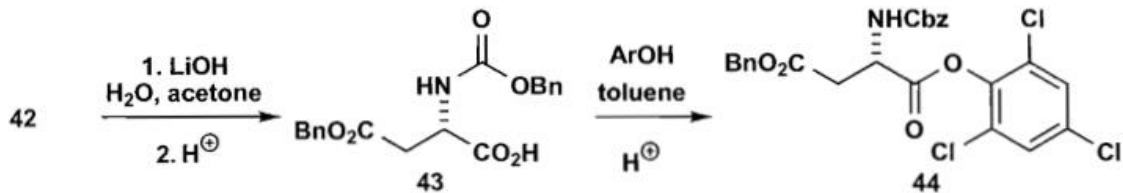
Both benzyl and Cbz groups are used in a synthesis of aspartame **38**, the dipeptide that is 150 times sweeter than sugar and used in many soft drinks under the name Nutrasweet™. Only one disconnection is reasonable: the amide bond in the middle of the molecule suggesting derivatives of available aspartic acid **39** and phenylalanine **40** as starting materials.



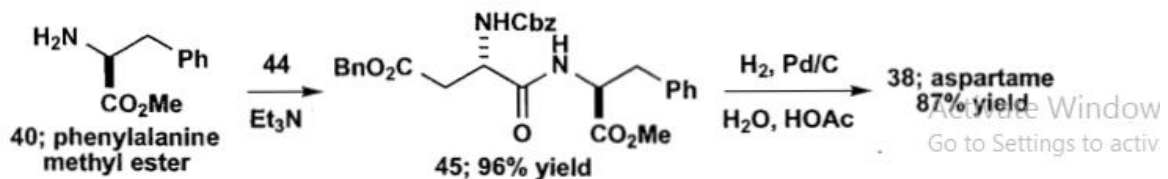
Since we need the methyl ester of phenylalanine, no further protection of that starting material is needed but the amino and one carboxylic acid group of aspartic acid need to be protected and the remaining acid activated. The Cbz group is perfect for the amino group and both acids in **41** can be esterified with benzyl alcohol.



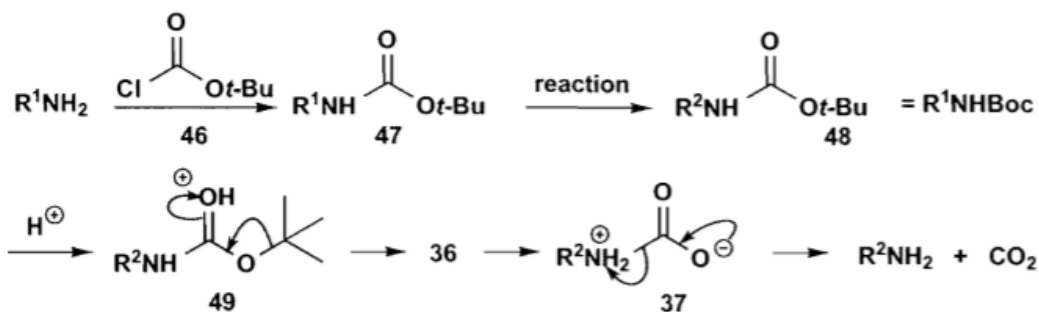
Now one ester must be cleaved and not the other. This looks difficult and cannot easily be done by hydrogenolysis but peptide chemists knew that the right one was hydrolysed in base to give the required intermediate **43**. Evidently the amide makes that ester more electrophilic but this was discovered by experience. Now the free acid must be activated towards nucleophilic attack: the trichlorophenyl ester **44** is ideal.⁶



The coupling requires only a weak base and the benzyl esters are removed by hydrogenation. The benzyl esters are there for protection but the trichlorophenyl ester is there for activation, making that ester more electrophilic than the benzyl ester in **44** or the methyl ester in **40**.



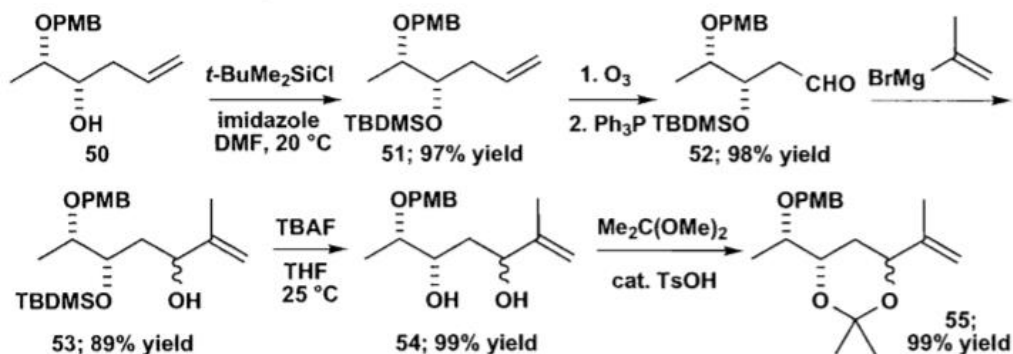
A close relative to Cbz is Boc (*t*-butyloxycarbonyl) that uses a different method to make esters easy to hydrolyse. It is added to an amine or an alcohol by the chloroformate **46** and, after the reaction, 'hydrolysed' with acid—no water being needed. The ester is protonated and the *t*-butyl cation drops out in an S_N1 reaction **49** to give the same intermediate **36** as in the removal of the Cbz group.



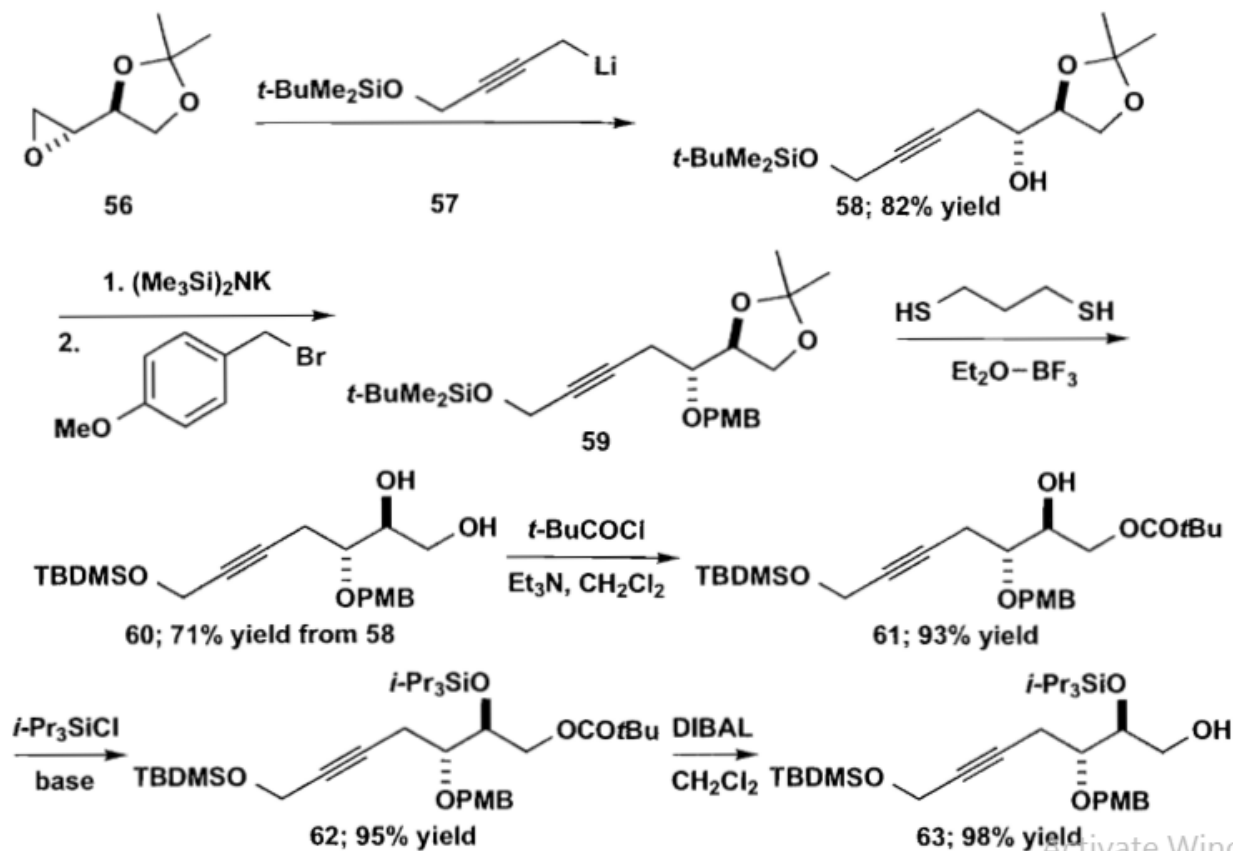
Protection of Alcohols

We have already mentioned the THP group but by far the most popular protecting groups for alcohols are the various silyl groups. You will already be familiar with the Me₃Si- or TMS (TriMethylSilyl) group but this is little used for protections as it falls off so easily, often just during chromatography. More hindered is the triethylsilyl (TES) or tri-*iso*-propylsilyl (TIPS) groups and *t*-butyldimethyl silyl (TBDMS or, misleadingly TBS) and, most hindered of them all, *t*-butyldiphenyl silyl (*t*-BuPh₂Si-). They are usually put on with the silyl chloride and a weak base, often imidazole in DMF, and they can be removed with oxygen nucleophiles, often in acid solution, and especially fluoride ion, often as TBAF (TetraButylAmmonium Fluoride Bu₄NF). This is particularly useful as fluoride is virtually unreactive towards most carbon atoms.

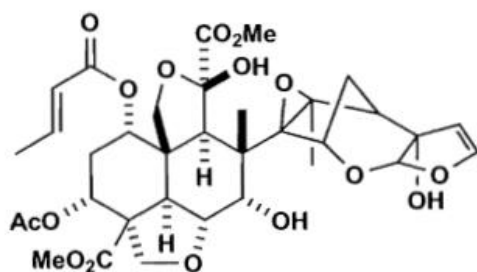
In Martin and Mulzer's synthesis⁷ of ephedrine B the starting material **50** already has a *p*-methoxybenzyl group on one alcohol. Protection of the other with a TBDMS group is *orthogonal* meaning that each group is removed under conditions that do not affect the other. Addition of isopropenyl Grignard to the aldehyde **52** creates a third alcohol **53** and now the TBAF group is removed so that an acetal **55** can be formed from the diol **54**. The yields are all good and eventually the PMB group will be removed by oxidation with a quinone.



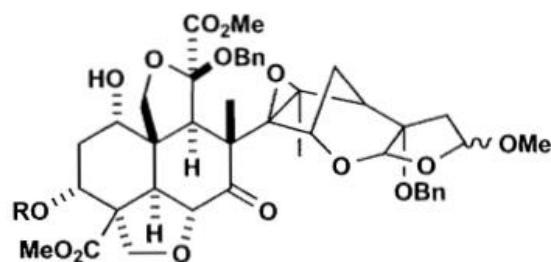
An intermediate in the synthesis of laulimalide by Davidson⁸ illustrates the differential protection of alcohols. The starting materials **56** and **57** already have an alcohol protected as a TBDMS silyl ether and a diol protected as an acetal. The alcohol in **58** is protected as a *p*-methoxybenzyl ether and the acetal 'hydrolysed' by acetal exchange to give the free diol **60**. Selective protection of the primary alcohol by a bulky acyl group (pivaloyl, *i*-BuCO-) **61** allows silylation of the secondary alcohol with a TIPS group **62**. Finally the pivaloyl group is selectively removed by DIBAL reduction to release just one free alcohol **63**.



Later on, all the protecting groups will be removed: the silyl groups with fluoride and the *p*-methoxybenzyl ether by oxidation with Ce(IV). In Ley's recently completed synthesis⁹ of azadirachtin **64** after 22 years of hard labour the key intermediate was **65**. You will notice benzyl ethers, acetals and a silyl ether. This is a more modern, one might almost say minimalist, use of protection. In an ideal world no protecting groups would be necessary but in a real synthesis they will almost certainly be required as we shall see in the rest of the book. But our aim should be to keep them to a minimum.



64; azadirachtin

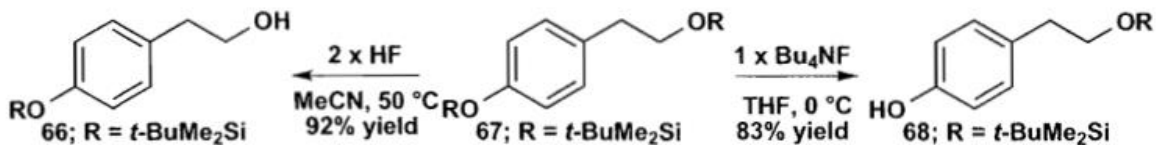


65; R = *t*-BuMe₂Si

The Literature on Protecting Groups

'Protecting groups' is a very large subject. There are hundreds of different protecting groups using scores of different ideas for every important functional group. It is particularly important that you refer to the literature before you choose which protecting group to use in a synthesis. It is a reasonable assumption that this rather dull subject would spawn some rather dull catalogue-like textbooks, and it has, but fortunately there is a glorious exception. Phil Kocienski's textbook¹⁰

Protecting Groups is comprehensive and entertaining. If you doubt this, have a look at page 644 (yes, it's also a long book). The extent of the subject is revealed by his chapter on protecting groups for alcohols with hundreds of protecting groups in the 176 pages and 686 references. This chapter is particularly good at selective protection and deprotection of, say, primary, secondary and tertiary alcohols. One example is the selective deprotection of either a phenol or an alcohol from the *bis*-silyl ether **67** using different reagents.¹¹



Protecting Group Summary

We cannot compete with large textbooks but here is a brief selection of simple protecting groups.

TABLE 9.1 Simple Protecting Groups (PGs) for some functional groups

Protecting Group	To Add	To Remove	PG resists	PG reacts with
Protecting Aldehydes RCHO and Ketones R₂CO				
Acetal (Ketal)	ROH or diol, H ⁺	H ⁺ , H ₂ O	nucleophiles, bases, reducing agents	electrophiles, oxidising agents
Protecting Carboxylic Acids RCO₂H				
Ester: RCO ₂ Me	CH ₂ N ₂	NaOH, H ₂ O	bases elec- trophiles	strong bases nucleophiles
Ester: RCO ₂ Et	EtOH, H ⁺	NaOH, H ₂ O		
Ester: RCO ₂ Bn	BnOH, H ⁺	H ₂ , cat or HBr		
Ester: RCO ₂ <i>t</i> -Bu	<i>t</i> -BuOH, H ⁺	H ⁺		
Anion: RCO ₂ ⁻	base	acid	nucleophiles	electrophiles
Protecting Alcohols ROH				
Ether: ROBn	PhCH ₂ Br, base	H ₂ , cat or HBr	see text	nucleophiles
Silyl ether	R ₃ SiCl, base	F ⁻ or H ⁺ , H ₂ O	see text	nucleophiles
Acetal: THP	DHP, H ⁺	H ⁺ , H ₂ O	bases	acids
Ester: ROCOR'	R'COCl, pyr	NH ₃ , MeOH	electrophiles	nucleophiles
Protecting Phenols ArOH				
Ether: ArOMe	Me ₂ CO ₃ , K ₂ CO ₃	HI, HBr or BBr ₃	bases	electrophiles
ArOCH ₂ OMe	MeOCH ₂ Cl/ base	HOAc, H ₂ O	bases	electrophiles
Protecting Amines RNH₂				
Amides RNHCOR'	RCOCl	NaOH or HCl in water	electrophiles	bases and nucleophiles
Urethanes RNHCO ₂ R'	ROCOCI	see text	electrophiles	bases and nucleophiles
Protecting Thiols RSH				
Thioester RSAC	AcCl, base	NaOH, H ₂ O	electrophiles	oxidation