

Lecture # 11

One Group C–C Disconnections I: Alcohols

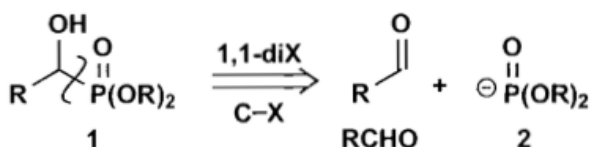
Background Needed for this Chapter

Using Organometallic Reagents to Make C–C Bonds.

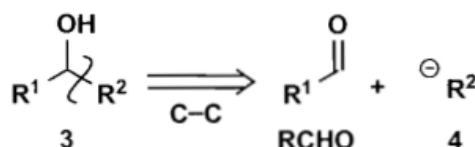
We now leave disconnections of bonds between carbon and other atoms (C–X disconnections) and turn to the more challenging C–C disconnections. These are more challenging because organic compounds contain many C–C bonds and it is not clear at first which ones should be disconnected. There is some very good news: the synthons that we met in chapter 6 for two-group C–X disconnections are the ones we shall use for one-group C–C disconnections. We start with an introduction to the three main types. In each case we shall replace one of the heteroatoms by a carbon unit 'R'.

For compounds with two heteroatoms joined to the same carbon, we used a 1,1-diX disconnection **1** removing one heteroatom to reveal a carbonyl compound, here an aldehyde, and a heteroatom nucleophile **2**. Replacing the heteroatom by R², we disconnect in the same way to reveal the same aldehyde and some nucleophilic carbon reagent **4**, probably R²Li or R²MgBr.

1,1-diX Disconnections:

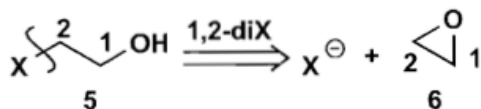


The Corresponding C–C Disconnection:

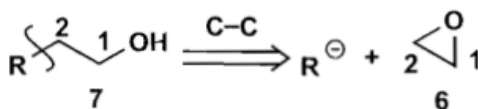


For compounds with a 1,2-relationship **5** we used an epoxide **6** at the alcohol oxidation level in combination with a heteroatom nucleophile. Disconnecting the corresponding C–C bond **7**, we use the same epoxide and a carbon nucleophile such as RLi or RMgBr.

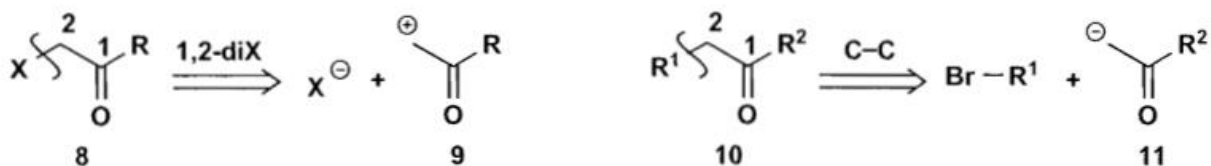
1,2-diX Disconnections:



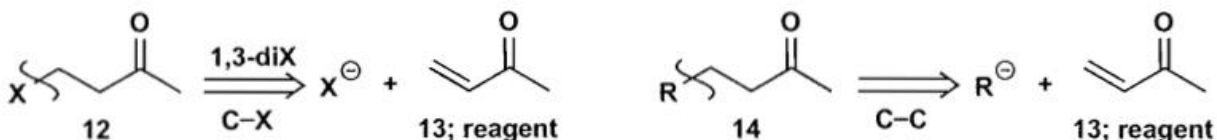
The Corresponding C–C Disconnection:



The same 1,2-diX relationship at the carbonyl level was disconnected **8** to give carbon electrophile **9**, probably an α-bromoketone, and a heteroatom nucleophile. Now we come to some more good news. We generally preferred nucleophilic heteroatoms but we can use nucleophilic or electrophilic carbon atoms whichever is better. Here we should much rather use the nucleophilic carbon synthon **11** as it is an enolate.

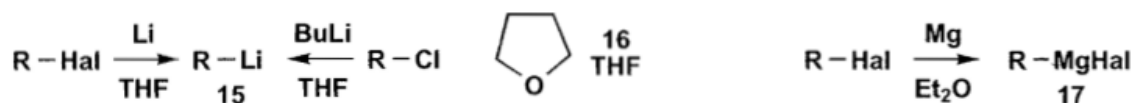


The 1,3-diX relationship **12** was quickly recognised as conjugate addition to the enone **13** in chapter 6. The corresponding C-C disconnection **14** uses the same enone **13** but the nucleophilic carbon species should be a copper derivative: RCu, R₂CuLi or RMgBr with Cu(I)Br.



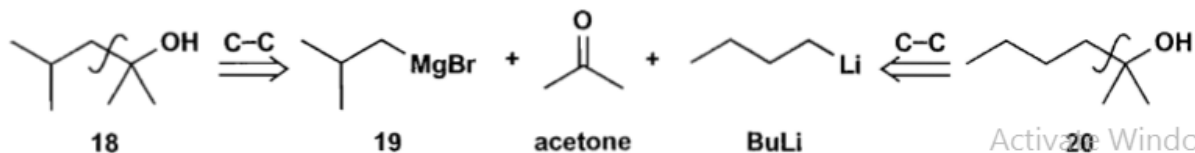
Reagents for Nucleophilic Carbon

The simplest unfunctionalised carbon nucleophiles (**15** and **17**) are made from alkyl halides with various metals such as Li(0) or Mg(0) or by exchange with available organometallic reagents such as butyl-lithium (BuLi) in anhydrous coordinating solvents like ether (Et₂O) or THF (tetrahydrofuran **16**). Enolates **11** are very important and will be discussed at length in later chapters.



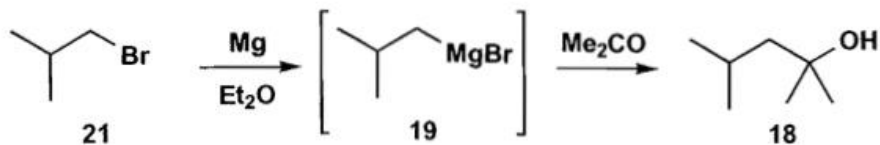
'1,1 C-C' Disconnections: The Synthesis of Alcohols

Disconnection **3** shows that any alcohol may be disconnected at a bond next to the OH group. Isomeric alcohols **18** and **20** can both be made from acetone using perhaps a Grignard reagent **19** in the first case and available BuLi in the second.



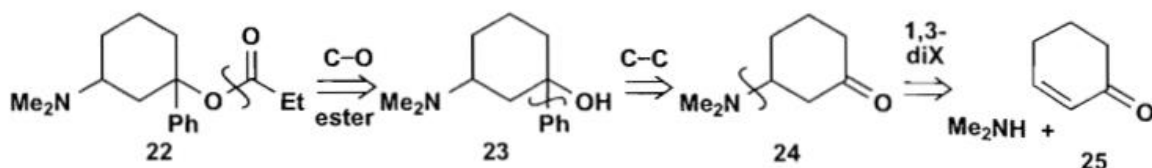
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The synthesis of **18** exemplifies the Grignard method. The reagent is made¹ from the alkyl halide with magnesium metal in dry ether and combined, without isolation, with the electrophile—all steps being carried out under strictly anhydrous conditions.

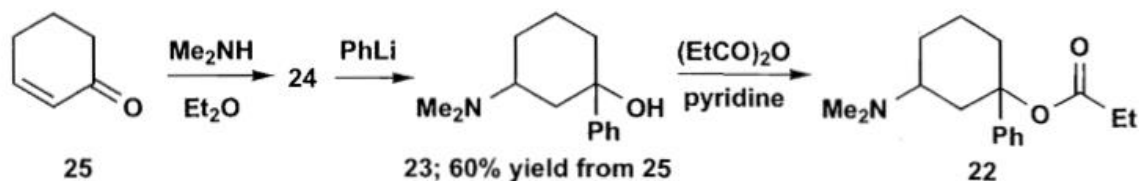


It may be necessary to disconnect structural C–X bonds before doing the C–C disconnection as with the aminoester wanted for evaluation as an analgesic.² Disconnecting the ester reveals

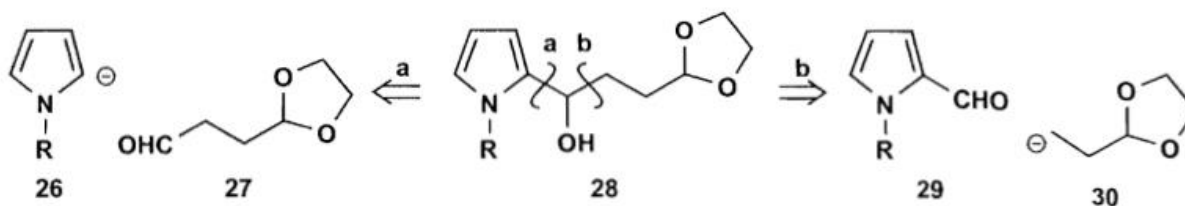
the tertiary alcohol **23** and removal of the phenyl group shows a hidden 1,3-diX relationship between ketone and amino groups **24**.



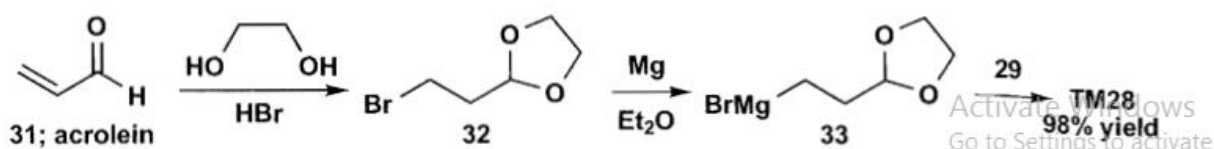
The synthesis is straightforward with available PhLi being used instead of a Grignard. The acylation of the tertiary benzylic alcohol **23** needs mild conditions to avoid dehydration.



In general there is a choice of which C–C bond should be disconnected and available starting materials may give a clue. We do not wish to disconnect the aromatic ring of the heterocyclic alcohol **28** so we can choose between bonds **a** and **b**.

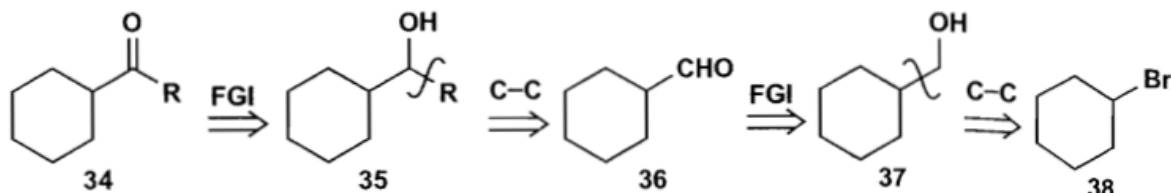


It turns out that both the aldehyde **29** and the easily made bromo-acetal **32** are commercially available and so route **b** was chosen³ with the protected Grignard reagent **33** as the carbon nucleophile (compare compound **10** in chapter 9).

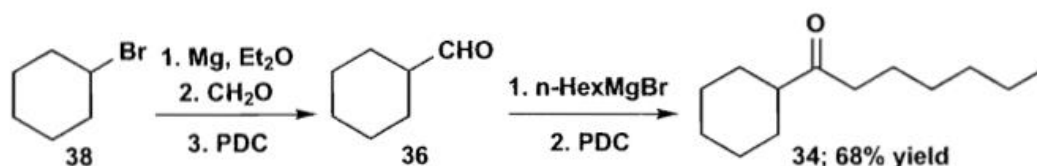


Aldehydes and Ketones

The simplest route to aldehydes and ketones using the same strategy is oxidation of an alcohol. So the analysis involves FGI back to the alcohol and then a C–C disconnection of one of the bonds next to the OH group. Lythgoe⁴ wanted to make a series of ketones **34** with various R groups to demonstrate a new alkyne synthesis. Disconnection of the C–R bond of the alcohol **35** meant that they could all be made from aldehyde **36** which can be made by the same strategy.



The oxidation of **35** presents no problems as over-oxidation cannot occur. But aldehyde **36** could be oxidised to the corresponding carboxylic acid so care was needed. In fact PCC (pyridinium chlorochromate: CrO₃ and HCl dissolved in pyridine) could be used for both.⁵



Direct addition of RMgBr or RLi to esters does not give ketones (see below) but addition to nitriles does⁶ (chapter 13).

Oxidising Agents for the Conversion of Alcohols to Aldehydes

The difficulty is over-oxidation. One simple solution is to oxidise all the way to the carboxylic acid and reduce selectively with, say DIBAL (*i*-Bu₂AlH). But the reagents in the table give reasonable results and can also be used for the oxidation of secondary alcohols to ketones.⁷ Full descriptions are in Fieser⁸ or the volume of *Comprehensive Organic Synthesis* devoted to oxidation.⁹

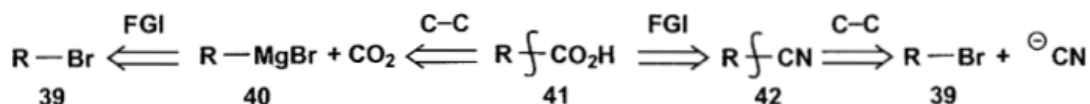
TABLE 10.1 Reagents for oxidising alcohols to aldehydes

Name	Reagents	For RCH ₂ OH to RCHO
–	Na ₂ Cr ₂ O ₇ , H ⁺	distil out RCHO as formed
Jones	CrO ₃ , H ₂ SO ₄ , acetone	distil out RCHO as formed
Collins	CrO ₃ , pyridine	use in CH ₂ Cl ₂ solution
PCC	CrO ₃ , pyridine.HCl	no modification needed
PDC	(pyridine.H ⁺) ₂ Cr ₂ O ₇	use in CH ₂ Cl ₂ solution
Swern	1. (COCl) ₂ , DMSO, 2. Et ₃ N	no modification needed

References for table: Na₂Cr₂O₇, H⁺: *Vogel*, p. 588, Collins,¹⁰ PCC,¹¹ PDC,¹¹ Swern.¹²

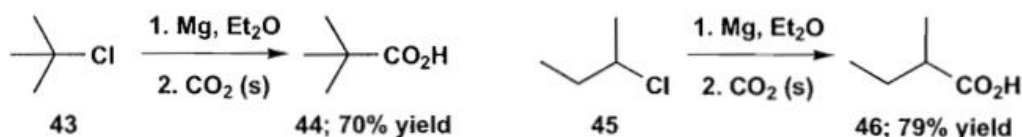
Carboxylic Acids

The same disconnection **41** can be used for carboxylic acids with CO₂ as the electrophile for a Grignard reagent **40**. Dry ice (solid CO₂) is particularly convenient for these reactions. Switching polarity by FGI to the nitrile **42**, the same disconnection now uses cyanide ion as the nucleophile but the same alkyl halide **39** that was used to make the Grignard reagent. Mechanistic considerations should decide between these alternatives.

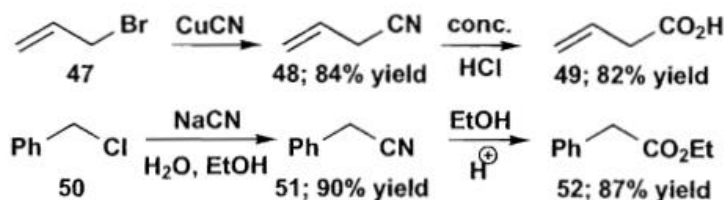


If the carboxyl group is attached to a tertiary, or even a secondary carbon atom, the S_N2 reaction with cyanide will not be so good and the carboxylation of a Grignard reagent is probably better. Pivalic acid **44** is available but can be made from *t*-BuCl in good yield.¹³ A detailed

procedure¹⁴ for the acid **46** describes how the acid is extracted from the ether with aqueous NaOH, separated from the water by neutralisation with HCl, and distilled.



If on the other hand the S_N2 reaction with cyanide is favoured, as with allylic **47** or benzylic **50** halides, that method is better.¹⁵ Hydrolysis of the nitrile **48** gives the acid **49** but treatment with an alcohol in acidic solution gives the ester **52** directly.¹⁶

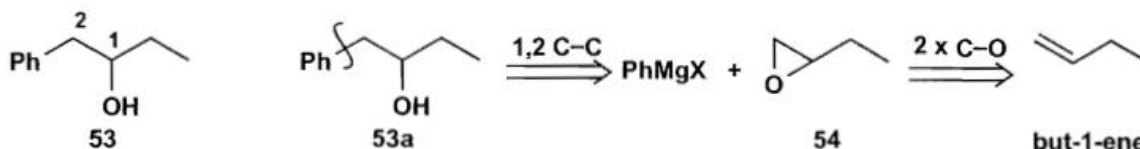


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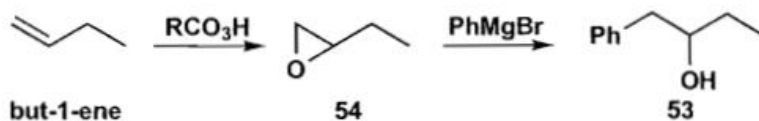
Acids can also be made by the oxidation of alcohols and acid derivatives are available from the acids via the acid chloride. Since acids can also be reduced to alcohols, there is a great deal of interdependence in all these methods. The synthesis of carbonyl compounds by one-group C–C disconnections is discussed more fully in chapter 13.

‘1,2 C–C’ Disconnections: The Synthesis of Alcohols

The analogy between this type of C–C disconnection and 1,2-diX disconnections was explained at the start of this chapter with compounds **5**, **6** and **7**. The epoxide route works particularly well if the epoxide is mono-substituted as the reaction with nucleophilic carbon should then be regioselective. Alcohol **53** is used in perfumery and can be disconnected **53a** at the next-but-one bond to the alcohol group with the idea of using the epoxide **54** made from the but-1-ene.



A Grignard or organo-lithium reagent would attack at the less hindered end of the epoxide and the Grignard route gives the alcohol **53**. In chapter 12 we shall see that this reaction is stereospecific.



We shall not extend the discussion on the 1,2-style of C–C disconnection as it is treated extensively, particularly at the carbonyl oxidation level, later in the book. We simply offer a table of the large number of derivatives that can be made from the alcohols we have been discussing in this and previous chapters. In all these cases, the first step would be FGI to the alcohol and then a C–C disconnection could be chosen.

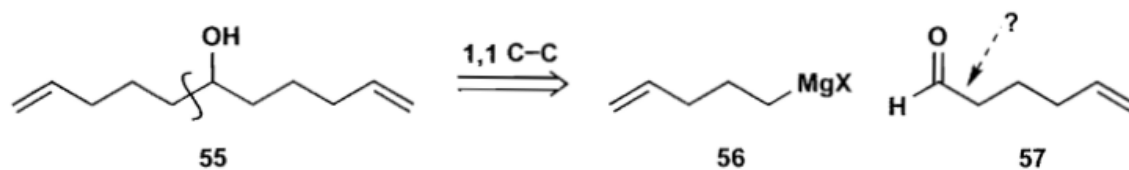
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TABLE 10.2 Compounds made from alcohols

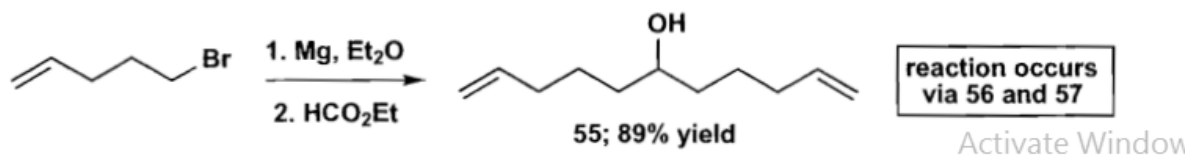
Reaction Type	Product	Chap	Further Products	Chap
Oxidation	aldehydes ketones acids	10	amines by reductive amination or reduction of amides	8
Esterification	esters	4	amines by reduction of amides	8
Tosylation	ROTs	4	other substitutions (see below)	4
HBr or PBr ₃	bromides	4	ethers, sulfides	4
SOCl ₂	chlorides	4	thiols	5
			nitriles	10

Example of the Synthesis of Alcohols and Related Compounds

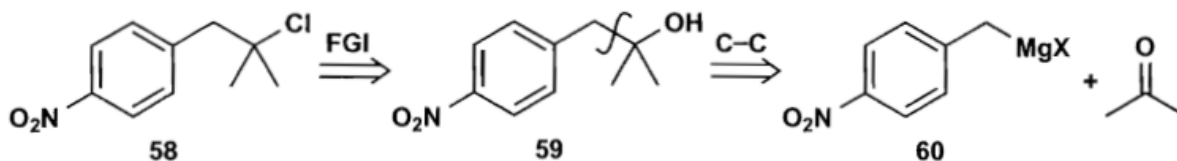
The alcohol **55** was needed for the synthesis of a bicyclic amine. Disconnection either side of the alcohol gives the aldehyde **57** and the Grignard **56** as starting materials.¹⁷ But could we not also disconnect the other side as well?



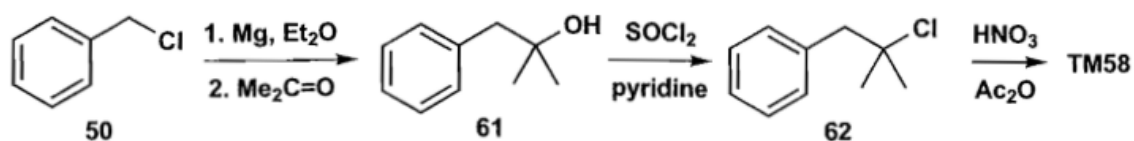
Symmetrical alcohols can in fact be made in one step from Grignard reagents and esters, as the reaction first produces the aldehyde **57** which is more electrophilic than the ester and so reacts again. There is a warning here! Aldehydes cannot be made by acylation of Grignard reagents with esters. But if two reactions are wanted, this is a good method.



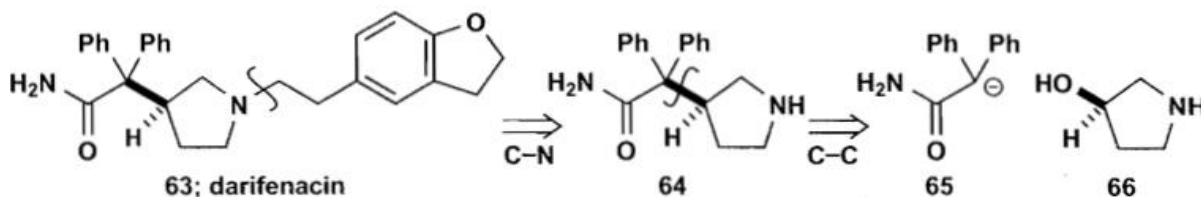
The tertiary chloride **58** was needed for a study of the effects of electron-withdrawing groups on the S_N1 reaction. FGI to the alcohol **59** suggests a C–C disconnection to a Grignard reagent **60** and acetone.



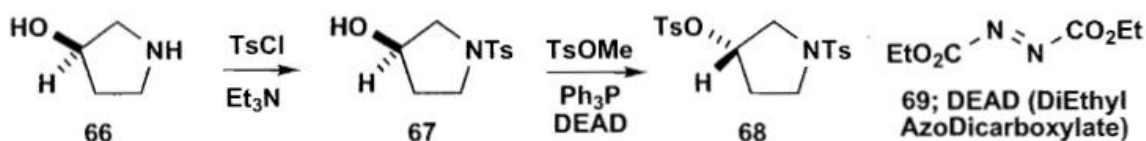
The nitro group must be introduced at some stage and the other substituent is always large and *ortho*, *para*-directing so it doesn't seem to matter when. As they wanted to make a series of compounds with electron-withdrawing groups on the benzene ring, they chose to make **62** as a common intermediate and nitrate last.¹⁸



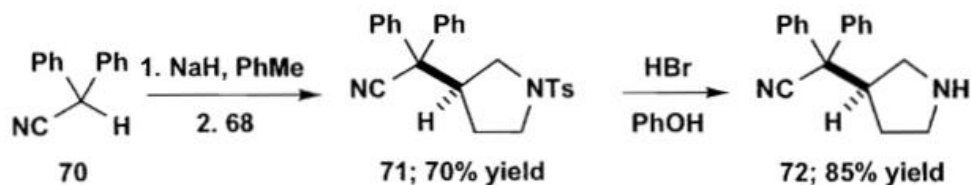
Darifenacin **63** is Pfizer's treatment for urinary urge incontinence. Disconnection at the C–N bond with some amine synthesis in mind (chapter 8) gives a much smaller heterocycle **64** that can again be disconnected in the middle with the idea of alkylating some enolate such as **65** with the derivative of an alcohol **66**. This is attractive because **66** is available as a single enantiomer cheaply from the amino acid hydroxyproline.¹⁹



There are two problems. Enolates of primary amides are not very practical as the NH protons are more acidic than the CH protons. The solution is to use the nitrile and hydrolyse it later to the amide. A more serious problem is that the S_N2 reaction we want to use to couple the two together will go with inversion and that will give the biologically inactive enantiomer of darifenacin. The solution is a double inversion. Protection of the amine by tosylation **67** is followed by tosylation of the alcohol with inversion using a Mitsunobu-style reaction. This unusual esterification goes reliably with inversion.²⁰

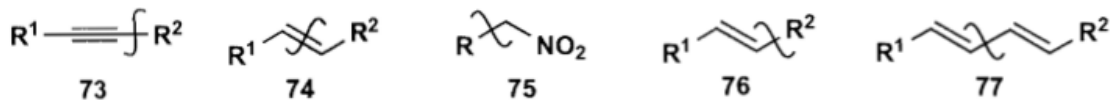


The nitrile **70** gives a stabilised anion with NaH that reacts with the tosylate with inversion as expected. The rather unusual sulfonamide deprotection with HBr in phenol gave the amine **72** that was coupled to the rest of the molecule as an amide. Reduction of the amide to the amine and, finally, hydrolysis of the nitrile to the amide gave darifenacin **63**.



Other One-Group C–C Disconnections

There are many other reactions that make C–C bonds using only one functional group. Among the most important involve alkynes by alkylation **73** (chapter 16), alkenes by the Wittig reaction **74** (chapter 15) and nitro compounds by alkylation **75** (chapter 22). Disconnections of alkenes outside the double bond **76** and especially disconnections of dienes between the double bonds **77** use palladium chemistry and are discussed extensively in *Strategy and Control*.



Carbon–Carbon Disconnections to Avoid

All the disconnections we have mentioned use functional groups to guide us. Nowhere will you find the disconnection of one alkyl group from another **78** without any functionality. It might seem that the reaction of a Grignard reagent **79** with an alkyl halide **80** would make **78**, and so it might. But these species will be in equilibrium with **81** and **82**. So, even if the coupling does work, we would get a mixture of **78** and both dimers. It is very much better to let functional groups guide your disconnections.

