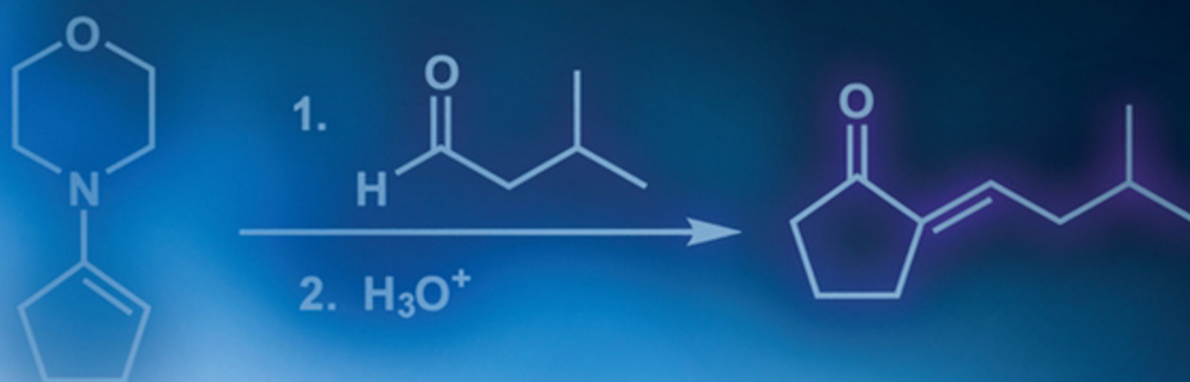


Stuart Warren · Paul Wyatt

# ORGANIC SYNTHESIS

## The Disconnection Approach

Second Edition

WILEY

# Organic Synthesis: The Disconnection Approach

# Organic Synthesis: The Disconnection Approach 2nd Edition

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The first edition was written with the active participation of
Denis Marrian who died in 2007. We dedicate this second edition to
Denis Haigh Marrian, 1920–2007, a great teacher and friend.

# Contents

# Preface

In the 26 years since Wiley published *Organic Synthesis: The Disconnection Approach* by Stuart Warren, this approach to the learning of synthesis has become widespread while the book itself is now dated in content and appearance. In 2007, Wiley published *Organic Synthesis: Strategy and Control* by Paul Wyatt and Stuart Warren. This much bigger book is designed as a sequel for fourth year undergraduates and research workers in universities and industry. The accompanying workbook was published in 2008. This new book made the old one look very dated in style and content and exposed gaps between what students were expected to understand in the 1980s and what they are expected to understand now. This second edition is intended to fill some of those gaps.

The plan of the original book is the same in the second edition. It alternates chapters presenting new concepts with strategy chapters that put the new work in the context of overall planning. The 40 chapters have the same titles: some chapters have hardly been changed while others have undergone a thorough revision with considerable amounts of new material. In most cases examples from recent years are included.

One source of new material is the courses that the authors give in the pharmaceutical industry. Our basic course is 'The Disconnection Approach' and the material we have gathered for this course has reinforced our attempts to give reasons for the synthesis of the various compounds which we believe enlivens the book and makes it more interesting for students. We hope to complete a second edition of the workbook shortly after the publication of the main text.

The first edition of the textbook was in fact the third in a series of books on organic chemistry published by Wiley. The first: *The Carbonyl Group: an Introduction to Organic Mechanisms*, published in 1974, is a programmed book asking for a degree of interaction with the reader who was expected to solve problems while reading. People rarely use programmed learning now as the method has been superseded by interactive programmes on computers. Paul Wyatt is writing an electronic book to replace *The Carbonyl Group* which will complete a package of an electronic book and books with associated workbooks in a uniform format that we hope will prove of progressive value as students of organic chemistry develop their careers.

**Stuart Warren and Paul Wyatt**
March 2008.

# General References

Full details of important books referred to by abbreviated titles in the chapters to avoid repetition.


Clayden, *Lithium*: J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, 2002.

Clayden, *Organic Chemistry*: J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, 2000.

*Comp. Org. Synth*.: eds. Ian Fleming and B. M. Trost, *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, six volumes.

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Fieser, *Reagents:* L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 20 volumes, 1967–2000, later volumes by T.-L. Ho.

Fleming, *Orbitals*: Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.

Fleming, *Syntheses*: Ian Fleming, *Selected Organic Syntheses*, Wiley, London, 1973.

Houben-Weyl; *Methoden der Organischen Chemie*, ed. E. Müller, and *Methods of Organic Chemistry*, ed. H.-G. Padeken, Thieme, Stuttgart, many volumes 1909–2004.

House: H. O. House, *Modern Synthetic Reactions*, Benjamin, Menlo Park, Second Edition, 1972.

Nicolaou and Sorensen: K. C. Nicolaou and E. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*. VCH, Weinheim, 1996. Second volume now published.

Saunders, *Top Drugs*: J. Saunders, *Top Drugs: Top Synthetic Routes*, Oxford University Press, Oxford, 2000.

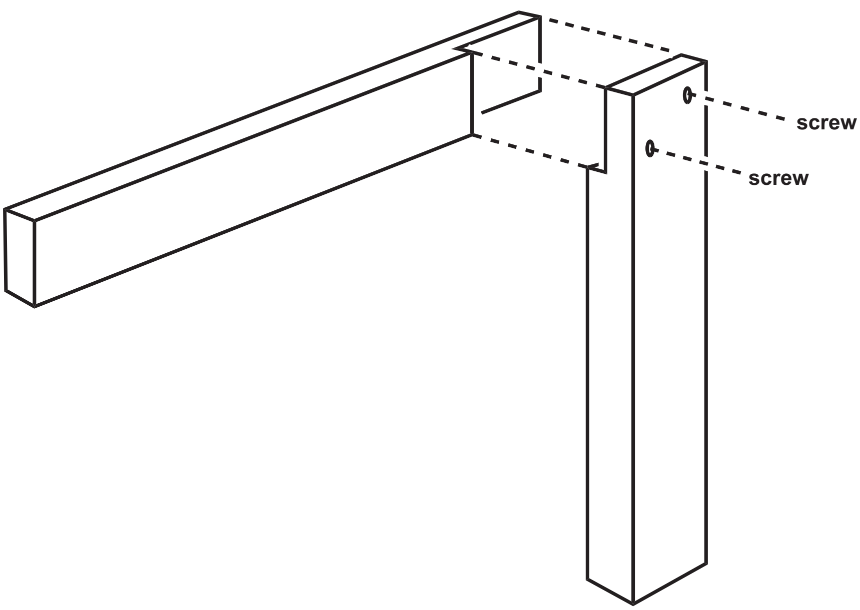
Strategy and Control; P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007 and *Workbook*, 2008.

Vogel: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Longman, Harlow, 1989.

# 1 The Disconnection Approach

This book is about making molecules. Or rather it is to help you design your own syntheses by logical and sensible thinking. This is not a matter of guesswork but requires a way of thinking backwards that we call the disconnection approach.

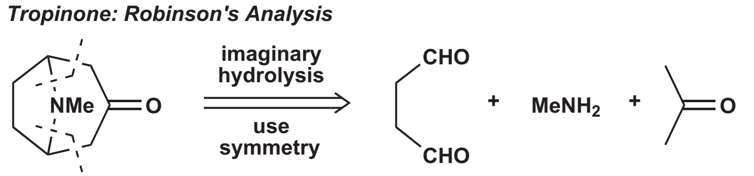
When you plan the synthesis of a molecule, all you know for certain is the structure of the molecule you are trying to make. It is made of atoms but we don't make molecules from atoms: we make them from smaller molecules. But how to choose which ones? If you wanted to make, say, a wooden joint, you would look in a do-it-yourself book on furniture and you would find an 'exploded diagram' showing which pieces you would need and how they would fit together.



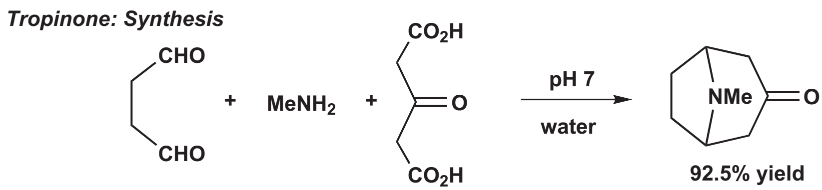

The disconnection approach to the design of synthesis is essentially the same: we 'explode' the molecule into smaller starting materials on paper and then combine these by chemical reactions. It isn't as easy as making wooden joints because we have to use logic based on our chemical knowledge to choose these starting materials. The first chemist to suggest the idea was Robert Robinson who published his famous tropinone synthesis[1] in 1917. His term was 'imaginary

*Organic Synthesis: The Disconnection Approach. Second Edition* Stuart Warren and Paul Wyatt

hydrolysis' and he put dashed lines across a tropinone structure.




This was a famous synthesis because it is so short and simple and also because it makes a natural product in a way that imitates nature. The reaction is carried out at pH 7 in water. In fact Robinson didn't use acetone, as suggested by his 'imaginary hydrolysis', but acetone dicarboxylic acid. This procedure is an improved one invented by Schöpf[2] in 1935.

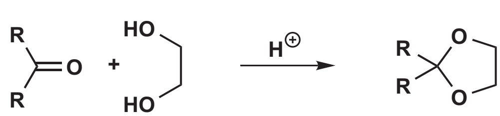



Amazingly, nobody picked up the idea until the 1960s when E. J. Corey at Harvard was considering how to write a computer program to plan organic syntheses.[3] He needed a systematic logic and he chose the disconnection approach, also called retrosynthetic analysis. All that is in this book owes its origin to his work. The computer program is called LHASA and the logic survives as a way of planning syntheses used by almost all organic chemists. It is more useful to humans than to machines.

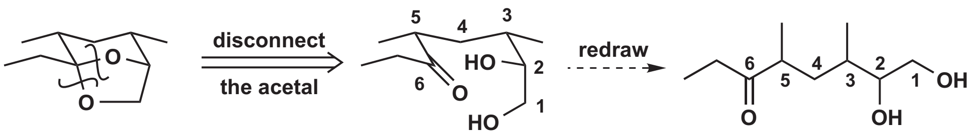
## The Synthesis of Multistriatin

Multistriatin **1** is a pheromone of the elm bark beetle. This beetle distributes the fungus responsible for Dutch elm disease and it was hoped that synthetic multistriatin might trap the beetle and prevent the spread of the disease. It is a cyclic compound with two oxygen atoms both joined to the same carbon atom (C-6 in **1**) and we call such ethers *acetals*.


We know one good way to make acetals: the reliable acid-catalysed reaction between two alcohols or one diol and an aldehyde or ketone.

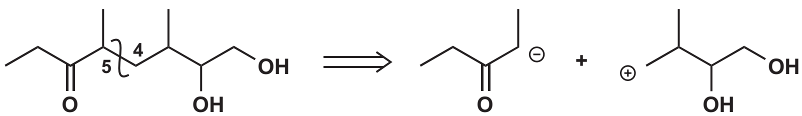



Intending to use this reliable reaction for our acetal we must disconnect the two C–O bonds to C–6 and reveal the starting material **2**, drawn first in a similar way to **1**, and then straightened out to look more natural **2a**. Numbering the carbon atoms helps to make sure **2** and **2a** are the same.



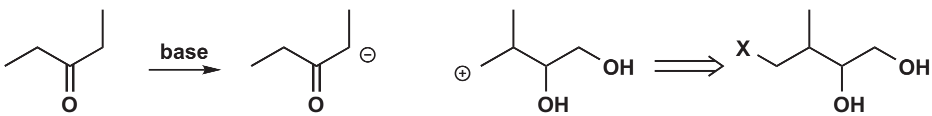

**2** **2a**

We now have a continuous piece of carbon skeleton with two OH groups and a ketone. No doubt we shall make this by forming a C–C bond. But which one? We know that ketones can form nucleophilic enolates so disconnecting the bond between C–4 and C–5 is a good choice because one starting material **3** is symmetrical. As we plan to use an enolate we need to make **3** nucleophilic and therefore **4** must be electrophilic so we write plus and minus charges to show that.



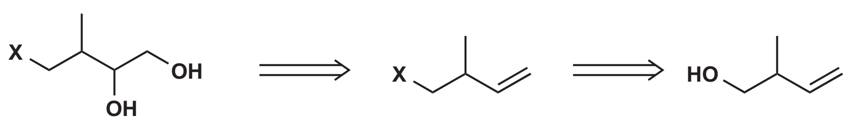

**2b** **3** **4**

Anion **3** can be made from the available ketone **5** but the only sensible way to make **4** electrophilic is to add a leaving group X, such as a halogen, deciding later exactly what to use.



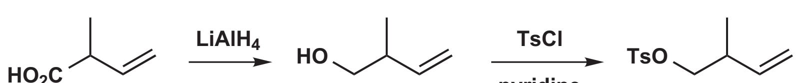

**5** **3** **4** **6; X = leaving group**

Compound **6** has three functional groups. One is undefined but the other two must be alcohols and must be on adjacent carbon atoms. There is an excellent reaction to make such a combination: the dihydroxylation of an alkene with a hydroxylating agent such as $OsO_4$. A good starting material becomes the unsaturated alcohol **7a** as that is known.



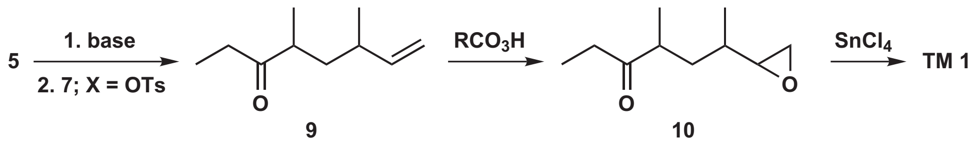

**6a; X = leaving group** **7** **7a**

In one synthesis[4] the alcohol **7a** was made from the available acid **8** and the leaving group (X in **6**) was chosen as tosylate (OTs; toluene-*p*-sulfonate).




**8** **7a** **7; X = OTs**

The two pieces were joined together by making the enolate of **5** and reacting it with **7**; X = OTs. The unsaturated ketone **9** was then oxidised with a peroxyacid to give the epoxide **10** and cyclisation with the Lewis acid $SnCl_4$ gave the target molecule (TM) multistriatin **1**.




You may have noticed that the synthesis does not exactly follow the analysis. We had planned to use the keto-diol **2b** but in the event this was a less practical intermediate than the keto-epoxide **10**. It often turns out that experience in the laboratory reveals alternatives that are better than the original plan. The basic idea—the strategy—remains the same.

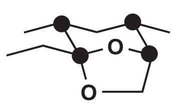
## Summary: Routine for Designing a Synthesis

1. *Analysis*
   (a) Recognise the functional groups in the target molecule.
   (b) Disconnect with known reliable reactions in mind.
   (c) Repeat as necessary to find available starting materials.
2. *Synthesis*
   (a) Write out the plan adding reagents and conditions.
   (b) Modify the plan according to unexpected failures or successes in the laboratory.

We shall develop and continue to use this routine throughout the book.

## What the Rest of the Book Contains

The synthesis of multistriatin just described has one great fault: no attempt was made to control the stereochemistry at the four chiral centres (black blobs in **11**). Only the natural stereoisomer attracts the beetle and stereoselective syntheses of multistriatin have now been developed.



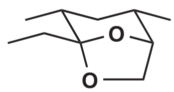

**11; chiral centres in multistriatin**

We must add stereochemistry to the list of essential background knowledge an organic chemist must have to design syntheses effectively. That list is now:

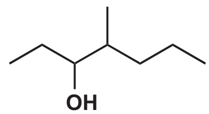
1. An understanding of reaction mechanisms.
2. A working knowledge of reliable reactions.
3. An appreciation that some compounds are readily available.
4. An understanding of stereochemistry.

Don't be concerned if you feel you are weak in any of these areas. The book will strengthen your understanding as you progress. Each chapter will build on whichever of the four points are relevant. If a chapter demands the understanding of some basic chemistry, there is a list of references at the start to chapters in Clayden *Organic Chemistry* to help you revise. Any other textbook of organic chemistry will have similar chapters.

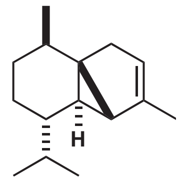
The elm bark beetle pheromone contains three compounds: multistriatin, the alcohol **12** and α-cubebene **13**. At first we shall consider simple molecules like **12** but by the end of the book we shall have thought about molecules at least as complex as multistriatin and cubebene.




**1; multistriatin**




**12**




**13; α-cubebene**

Multistriatin has been made many times by many different strategies. Synthesis is a creative science and there is no 'correct' synthesis for a molecule. We shall usually give only one synthesis for each target in this book: you may well be able to design shorter, more stereochemically controlled, higher yielding, more versatile—in short better—syntheses than those already published. If so, you are using the book to advantage.

## References

1. R. Robinson, *J. Chem. Soc.*, 1917, **111**, 762.
2. C. Schöpf and G. Lehmann, *Liebig's Annalen*, 1935, **518**, 1.
3. E. J. Corey, *Quart. Rev.*, 1971, **25**, 455; E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.
4. G. T. Pearce, W. E. Gore and R. M. Silverstein, *J. Org. Chem.*, 1976, **41**, 2797.

# 2 Basic Principles: Synthons and Reagents Synthesis of Aromatic Compounds

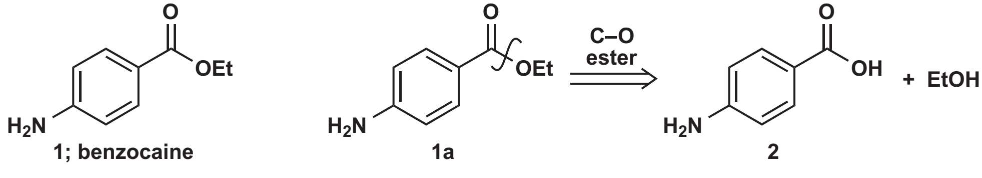
**Background Needed for this Chapter** References to Clayden, *Organic Chemistry:*
Electrophilic aromatic substitution; chapter 22. (Electrophilic Aromatic Substitution)
Nucleophilic aromatic substitution: chapter 23 (Electrophilic Alkenes).
Reduction: chapter 24 (Chemoselectivity: Selective Reactions and Protection).

## Synthesis of Aromatic Compounds

The benzene ring is a very stable structural unit. Making aromatic compounds usually means adding something(s) to a benzene ring. The disconnection is therefore almost always of a bond joining a side chain to the benzene ring. All we have to decide is when to make the disconnection and which reagents to use. You will meet the terms *synthon* and *functional group interconversion* (FGI) in this chapter.

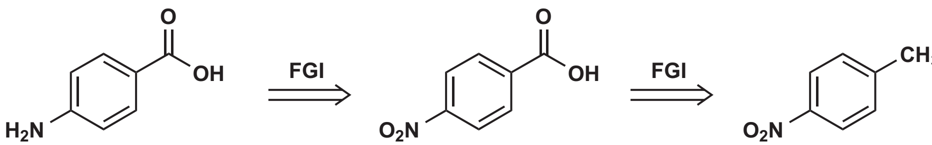
## Disconnection and FGI

You already know that disconnections are the reverse of known reliable reactions so you should not make a disconnection unless you have such a reaction in mind. In designing a synthesis for the local anaesthetic benzocaine **1**, we see an ester group and know that esters are reliably made from some derivative of an acid (here **2**) and an alcohol (here ethanol). We should disconnect the C–O ester bond. From now on we will usually write the reason for a disconnection or the name of the forward reaction above the arrow.



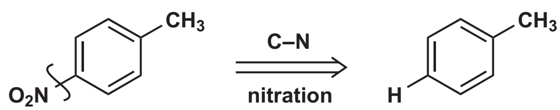

The sign for a disconnection on a molecule is some sort of wiggly line across the bond being disconnected. You can draw this line in any way you like within reason. The 'reaction arrow' is the 'implies' arrow from logic. The argument is that the existence of any ester *implies* that it can be made from an acid and an alcohol.

We should now like to disconnect either the $NH_2$ or the $CO_2H$ group but we know of no good reactions corresponding to those disconnections. We need to change both groups into some other groups that can be added to a benzene ring by a known reliable reaction. This process is called *functional group interconversion* or FGI for short and is an imaginary process, just like a disconnection. It is the reverse of a real reaction. Here we know that we can make amino groups by reduction of nitro groups and aryl carboxylic acids by oxidation of alkyl groups. The FGIs are the reverse of these reactions.



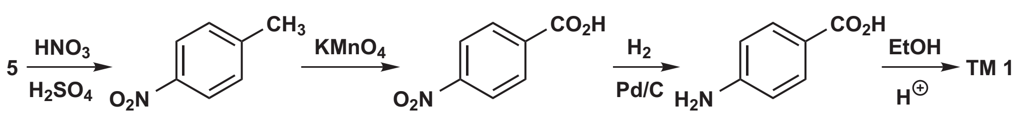

2 3 4

We 'oxidised' the amino group first and 'reduced' the acid second. The order is unimportant but is something we come back to in the forward reaction. What matters is that we have found a starting material **4** that we know how to make. If we disconnect the nitro group **4a** we shall be left with toluene **5** and toluene can be nitrated in the *para*-position with a mixture of nitric and sulfuric acids.




4a 5; toluene

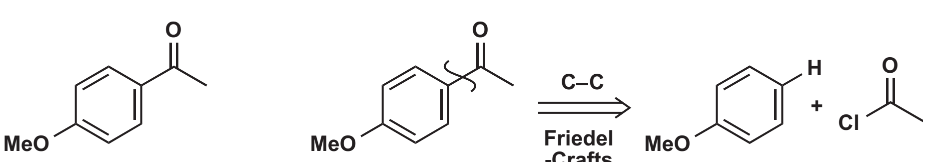
Now we should write out the synthesis. You cannot of course predict exactly which reagents and conditions will be successful and no sensible organic chemist would attempt to do this without studying related published work. It is enough to make suggestions for the type of reagent needed. We shall usually give the reagents used in the published work and conditions where they seem to matter. Here it is important to nitrate first and oxidise second to get the right substitution pattern.[1]




4 3 2

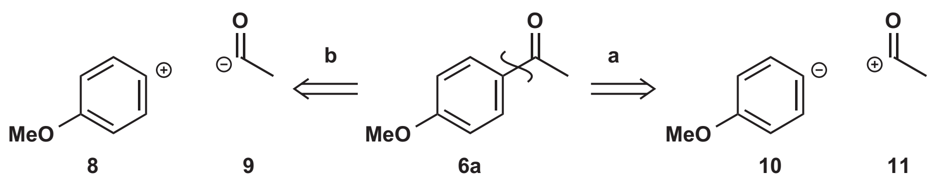
## Synthons Illustrated by Friedel-Crafts Acylation

The useful disconnection **6a** corresponds to Friedel-Crafts acylation of aromatic rings and is the obvious one on the ketone **6** having the perfume of hawthorn blossom. Reaction[2] of ether **7** with MeCOCl and $AlCl_3$ gives **6** in 94–96% yield—a good reaction indeed.

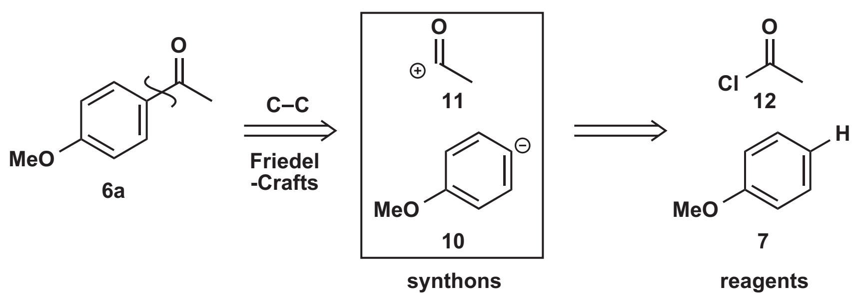



6 6a 7

In both this reaction and the nitration of toluene we used to make benzocaine, the reagent is a cation: $MeCO^+$ for the Friedel-Crafts and $NO_2{}^+$ for the nitration. Our first choice on disconnecting a bond to a benzene ring is to look for a cationic reagent so that we can use electrophilic aromatic substitution. We know not only which bond to break but also in which sense electronically to break it. In principle we could have chosen either polarity from the same disconnection: **a** (we actually chose) or **b** (we did not).

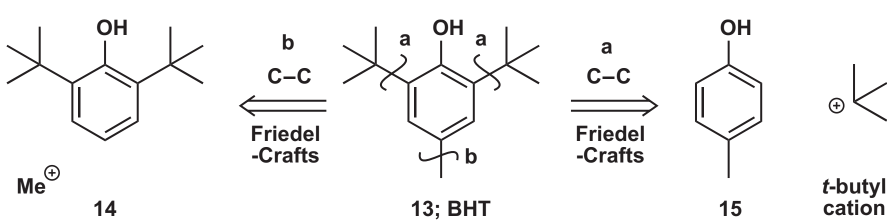



The four fragments **8–11** are *synthons*—that is idealised ions that may or may not be involved in the actual reaction but help us to work out which reagent to choose. As it happens, synthon **11** is a real intermediate but the others are not. For an anionic synthon like **10** the reagent is often the corresponding hydrocarbon as $H^+$ is lost during the reaction. For a cationic synthon like **11** the reagent is often the corresponding halide as that will be lost as a leaving group during the reaction. It is a matter of personal choice in analysing a synthesis problem whether you draw the synthons or go direct to the reagents. As you become more proficient at retrosynthetic analysis, you will probably find that drawing the synthons becomes unnecessary and cumbersome.

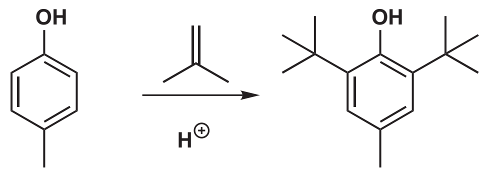



## Synthons Illustrated by Friedel-Crafts Alkylation

Friedel-Crafts alkylation is also useful though less reliable than acylation. With that in mind, we could disconnect BHT **13** ('Butylated Hydroxy-Toluene') at either bond **b** to remove the methyl group or bond **a** to remove both *t*-butyl groups. There are various reasons for preferring **a**. *para*-Cresol **15** is available whereas **14** is not. The *t*-butyl cation is a much more stable intermediate than the methyl cation—and *t*-alkylations are among the most reliable. Finally the OH group is more powerfully *ortho*-directing than the methyl group.



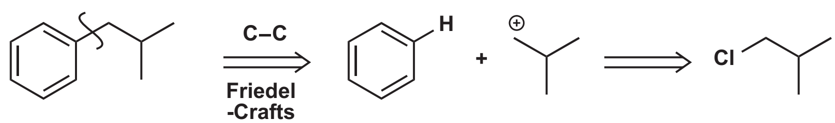
We have a choice of reagents for the *t*-butyl cation: a halide with Lewis acid catalysis, and *t*-butanol or isobutene with protic acid catalysis. The least wasteful is the alkene as nothing is lost. Protonation gives the *t*-butyl cation and two *t*-butyl groups are added in one operation.[3]




15 13; BHT

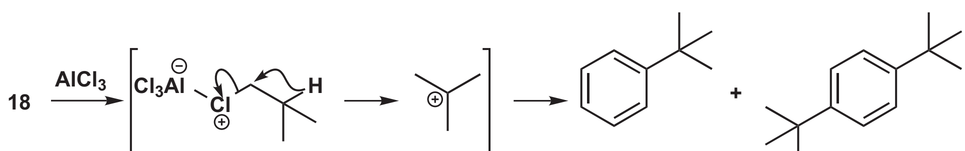
## Functional Group Addition Illustrated by Friedel-Crafts Alkylation

Attempting Friedel-Crafts alkylation with primary halides often gives the 'wrong' product by rearrangement of the intermediate cation. If we want to make *i*-butylbenzene **16**, it seems obvious that we should alkylate benzene with an *i*-butyl halide, e.g. **18** and $AlCl_3$.



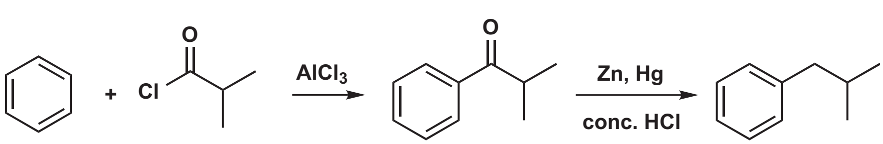

16; *i*-butylbenzene 17 18

This reaction gives two products **21** and **22** but neither contains the *i*-butyl group. Both contain instead the *t*-butyl group. The intermediate complex rearranges by hydride shift **19** into the *t*-butyl cation **20** as the primary cation **17** is too unstable.



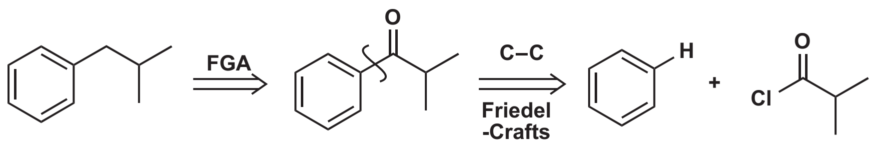

19 20 21 22

Polyalkylation was an advantage in the synthesis of BHT **13**: it is the rearrangement that is chiefly unacceptable here. Friedel-Crafts acylation avoids both problems. The acyl group does not rearrange and the product is deactivated towards further electrophilic attack by the electron-withdrawing carbonyl group. We have an extra step: reduction of the ketone to a $CH_2$ group. There are various ways to do this (see chapter 24)—here the Clemmensen reduction is satisfactory.[4]




23 24 TM 16

The preliminary to the corresponding disconnection is the 'addition' (imaginary) of a functional group where there was none. We call this FGA (functional group addition). The corresponding known reliable reaction is the removal of the functional group. We could put the carbonyl group anywhere but we put it next to the benzene ring as it then allows us to do a reliable disconnection.

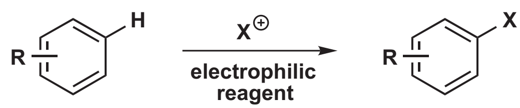



**TM 16** **24** **23**

## Reliable Reagents for Electrophilic Substitution

Table 2.1 summarises the various reagents we have mentioned (and some we haven't). Full details of mechanisms, orientation and applications appear in *Clayden* chapter 22.

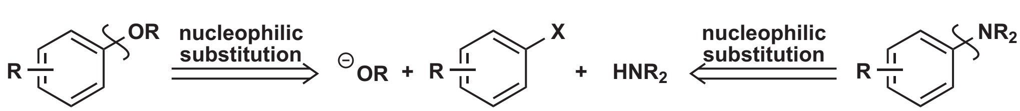
**TABLE 2.1** Reagents for aromatic electrophilic substitution




| Synthon | Reagent | Reaction | Comments |
|---|---|---|---|
| $R^+$ | $RBr + AlCl_3$ | Friedel-Crafts | good for *t*-alkyl |
| | ROH or alkene $+H^+$ | alkylation[5] | OK for *s*-alkyl |
| $RCO^+$ | $RCOCl + AlCl_3$ | Friedel-Crafts acylation | very general |
| $NO_2^+$ | $HNO_3 + H_2SO_4$ | nitration | very vigorous |
| $Cl^+$ | $Cl_2 + FeCl_3$ | chlorination | other Lewis acids used too |
| $Br^+$ | $Br_2 + Fe\ (=FeBr_3)$ | bromination | other Lewis acids used too |
| $^+SO_2OH$ | $H_2SO_4$ | sulfonation | may need fuming $H_2SO_4$ |
| $^+SO_2Cl$ | $ClSO_2OH + H_2SO_4$ | chloro-sulfonation | very vigorous |
| $ArN_2^+$ | $ArNH_2 + HONO$ | diazo-coupling | product is $Ar^1N{=}NAr^2$ |

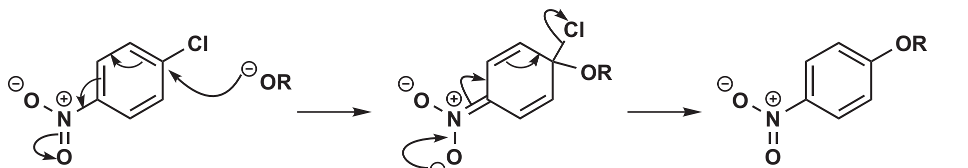
## Changing the Polarity: Nucleophilic Aromatic Substitution

If we make the same disconnections as before **25** and **27** but change the polarity we need electrophilic aromatic rings and nucleophilic reagents. We shall need a leaving group X (might be a halogen) on the aromatic ring **26** and reagents such as alkoxides or amines.



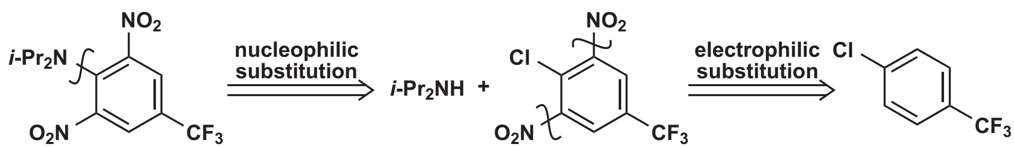

**25** **26** **27**

The nucleophilic reagents are behaving normally for alcohols or amines but the aromatic electrophiles present a problem. Benzene rings are nucleophilic, if weakly, but are not electrophilic at all. There is no $S_N2$ reaction on an aryl halide. To get the reactions we want, we must have *ortho*- or *para*-electron-withdrawing groups such as $NO_2$ or C=O to accept the electrons as the nucleophile adds **28** to form **29**.



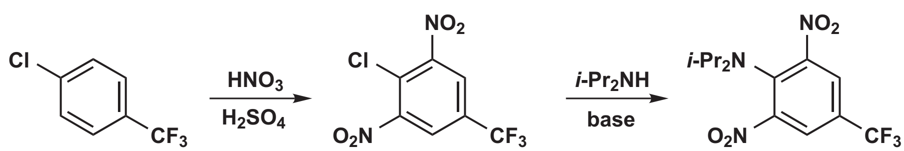

**28** **29** **30**

Fortunately, nitro groups go in the right positions (i.e. *ortho* and *para* but not *meta*) by direct nitration of, say, chlorobenzene. So we can be guided in our choice of polarity by the nature of the target molecule. The Lilly pre-emergent herbicide trifluralin B **31** has three electron-withdrawing groups: two nitro and one $CF_3$, *ortho*- and *para*- to the amine, ideal for nucleophilic substitution on **32**. The nitro groups can be introduced by nitration as Cl directs *ortho*, *para* while $CF_3$ directs *meta*.




**31** **32** **33**

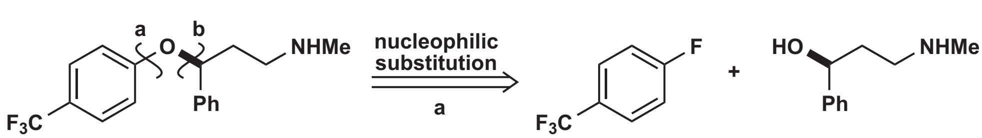
The synthesis[5] is simplicity itself, as the synthesis of any agrochemical must be. The base in the second step is to remove the HCl produced in the reaction, not to deprotonate the amine.




**33** **32** **31**

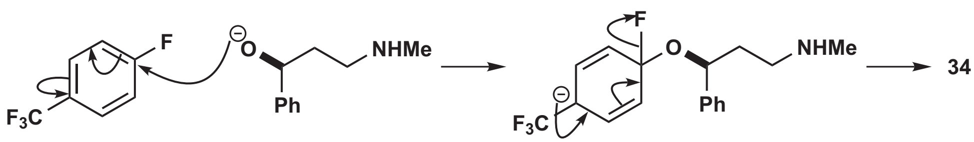
## Thinking Mechanistically

It is obvious that the choice between nucleophilic and electrophilic substitution must be mechanistically made but this is generally true of the choice of all disconnections, synthons and reagents. The formation of **31** was easy because the aryl chloride was activated by three groups. In the synthesis of fluoxetine (Prozac), a rather widely taken anti-depressant, aryl ether **34** is an essential intermediate.[6] Though disconnection **b** looks attractive, as a simple $S_N2$ reaction should work well, disconnection **a** was preferred because **34** must be a single enantiomer and enantiomerically pure alcohol **36** was available.




**34** **35** **36**

You should have been surprised to see fluoride as the leaving group. Fluoride is the worst leaving group among the halogens as the C–F bond is very strong: it is rare to see an $S_N2$ reaction with fluoride as the leaving group. Yet it is the best choice for nucleophilic aromatic substitution especially when the ring is only weakly activated as here with just one $CF_3$ group. In this two-step reaction, the difficult step is the addition of the nucleophile: aromaticity is destroyed and the intermediate is an unstable anion. The second step **38** is fast. Fluorine accelerates the first step as it is so electronegative and it doesn't matter that it hinders the second step as that is fast anyway.

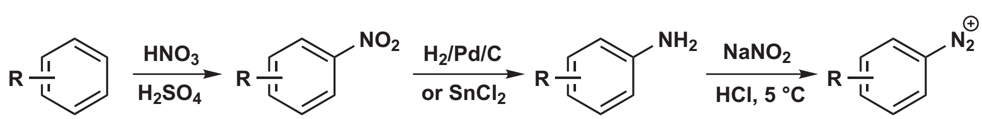



**37** **38**

You may have noticed something else. The formation of trifluralin **31** showed that amines are good nucleophiles for nucleophilic aromatic substitution and the nucleophile here is an amino-alcohol **36**. Direct reaction with **36** might lead to the formation of an amine instead of an ether. To avoid this, **36** is first treated with NaH to make the oxyanion and then added to **35**. The alcohol is less nucleophilic but the oxyanion is more nucleophilic than the amine. We hope you now see why an understanding of reaction mechanisms is an essential preliminary to the designing of syntheses.

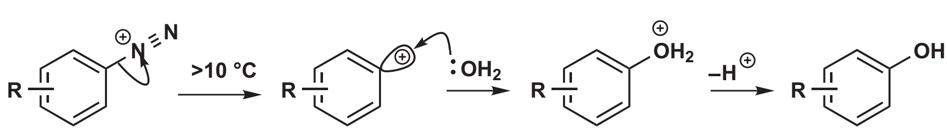
## Changing the Polarity: Nucleophilic Aromatic Substitution by the $S_N1$ Mechanism

Though the $S_N2$ mechanism is not available for aromatic nucleophilic substitutions, the $S_N1$ is providing we use the very best leaving group available. This is a molecule of nitrogen released from a diazonium salt **42** on gentle warming. A standard sequence is nitration of an aromatic compound **39** to give **40**, reduction to the amine **41** and diazotisation with $NaNO_2$/HCl to give the diazonium salt **42**. Nitrous acid HONO is the true reagent giving $NO^+$ that attacks at nitrogen.



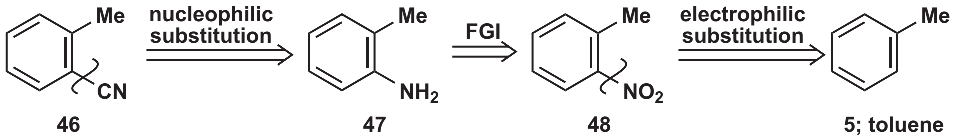

**39** **40** **41** **42**

The diazonium salt **42** is stable at 0–5 °C but decomposes to $N_2$ and an unstable aryl cation **43** on warming to room temperature. The empty orbital of **43** is in an $sp^2$ orbital in the plane of the aromatic ring, quite unlike the normal p orbital for cations like **20**. Reaction occurs with any available nucleophile, even water, and this is a route to phenols **45**.




**42a** **43** **44** **45**

This route is particularly valuable for substituents that cannot easily be added by electrophilic substitution such as OH or CN. Table 2.2 gives you a selection of reagents. For the addition of CN, Cl or Br, copper (I) derivatives usually give the best results. So the aryl nitrile **46** might come from amine **47** via a diazonium salt and routine disconnections lead us back to toluene.




The synthesis is straightforward.[7] In the laboratory you would not have to carry out the first two steps as the amine **47** can be bought. Industry makes it on a large scale by this route. Notice that we do not draw the diazonium salt. You can if you want, but it is usual to show two steps carried out without isolation of the intermediate in this style: 1. reagent A, 2. reagent B. This makes it clear that all the reagents are not just mixed together. Another style is used in Table 2.2: the reactive intermediate is in square brackets. But it is helpful to show conditions for the diazotisation as temperature control is important.

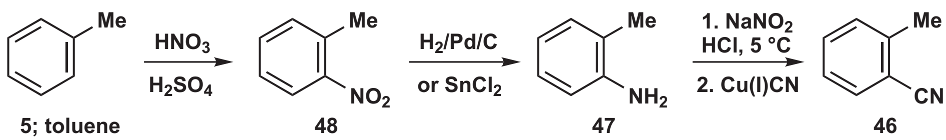
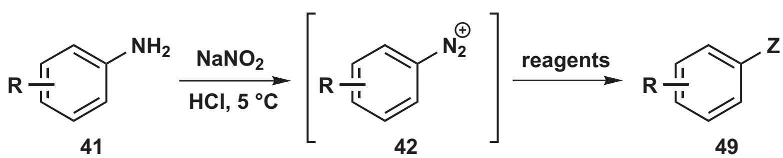


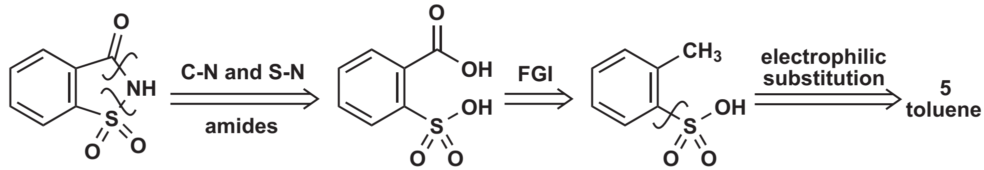

**TABLE 2.2** Reagents for aromatic nucleophilic substitution on $ArN_2^+$




| Synthon | Reagents | Comments |
|---|---|---|
| –OH | water | probably $S_N1$ |
| –OR | alcohol ROH | probably $S_N1$ |
| –CN | Cu(I)CN | may be a radical reaction |
| –Cl | Cu(I)Cl | may be a radical reaction |
| –Br | Cu(I)Br | may be a radical reaction |
| –I | KI | best way to add iodine |
| –Ar | ArH | Friedel-Crafts arylation |
| –H | $H_3PO_2$ or $EtOH/H^+$ | reduction of $ArN_2^+$ |

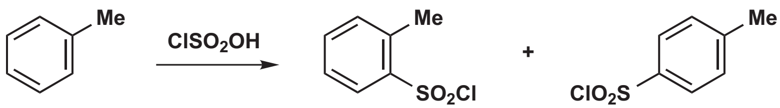
## *ortho- and para- Product Mixtures*

We used the nitration of toluene to give both the *para*-nitro **4** and the *ortho*-nitro compounds **48**. In fact the reaction gives a mixture. This is acceptable providing the compounds can be separated and especially so if industry does the job on a very large scale, as here. The synthesis of the sweetener saccharine is a good example. Saccharine **50** is a cyclic imide: that is a double amide from one nitrogen atom and two acids. If we disconnect the C–N and S–N bonds the two acids—one carboxylic and one sulfonic—are revealed **51**. Both groups are *meta*-directing so we must do FGI to convert one of them into an *ortho,para*-directing group and we can use the same oxidation reaction we met at the start of the chapter (**4** to **3**). Now **52** can be made by sulfonation.



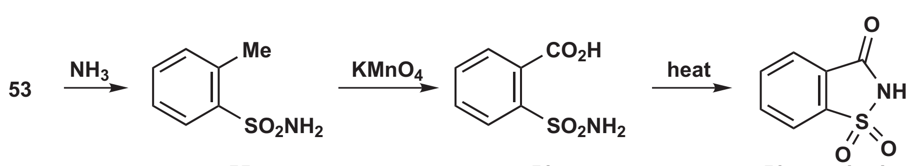

**50; saccharine** **51** **52**

In practice chloro-sulfonic acid is used as this gives the sulfonyl chloride directly. You may be surprised at this, thinking that Cl might be the best leaving group. But there is no Lewis acid here. Instead the very strong chloro-sulfonic acid protonates itself to provide a molecule of water as leaving group (see workbook).




**5; toluene** **53** **54**

The reaction gives a mixture of the *ortho*- **53** and *para*- **54** products. The *ortho*-compound is converted into saccharine by reaction with ammonia and oxidation and the *para*-compound toluene-*p*-sulfonyl chloride **54**, or tosyl chloride, is sold as a reagent for converting alcohols into leaving groups.




**55** **56** **50; saccharine**

## References

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