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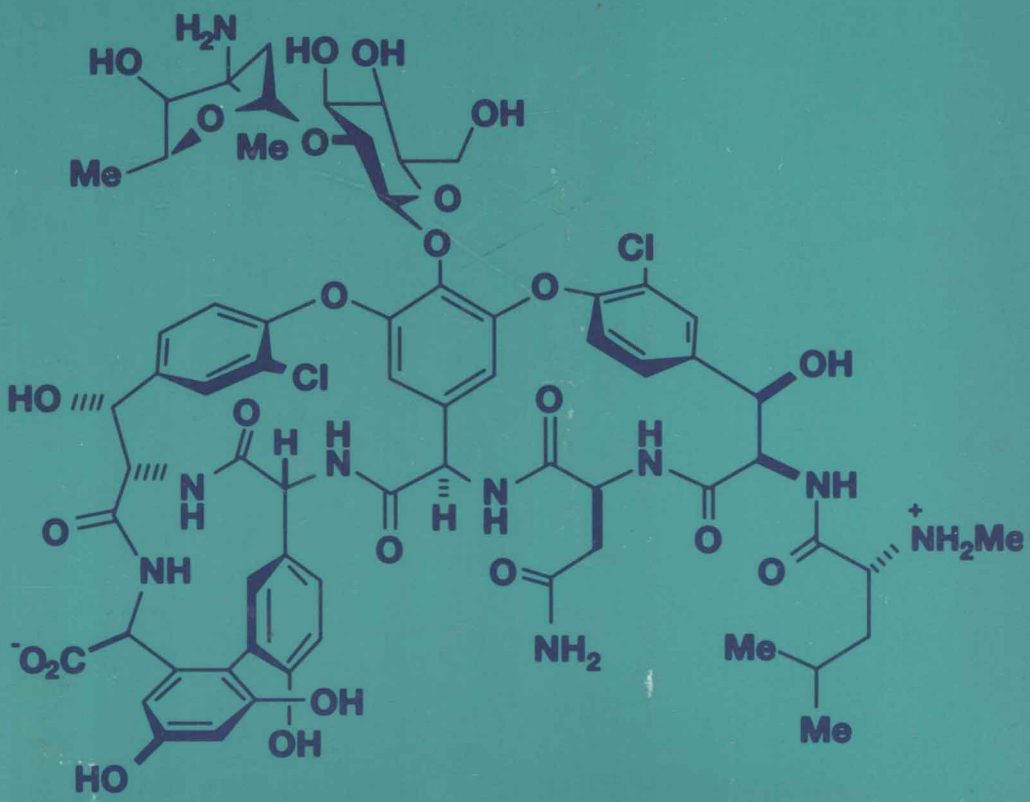
ASYMMETRIC SYNTHESIS

GARRY PROCTER



Asymmetric Synthesis

Garry Procter

Department of Chemistry and Applied Chemistry
University of Salford

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Preface

Molecular asymmetry has been a topic of great interest to chemists, and organic chemists in particular, for many years. The consequences of such asymmetry in the structure of molecules pervade many areas of daily life. For example, the interaction between one chiral molecular species and another can be important in such apparently diverse properties as the smell of a fruit and the antibacterial activity of a drug. It is not surprising then that many chemists interested in organic synthesis find the challenge of preparation of single enantiomers of such chiral molecules, asymmetric synthesis, both interesting and rewarding.

Given the importance of molecular asymmetry in Nature and in industry, the topic of asymmetric synthesis is finding its way increasingly into undergraduate chemistry courses. It is my involvement in just such a course which is responsible for this book. It is my hope that this book will be of some use to those involved in the preparation and teaching of such courses, and to the students themselves. In addition, research workers starting out in this area might also find it of some interest. With this in mind, I have tried to keep the 'jargon' to a minimum, and to keep the stereochemical descriptions as simple as possible. I expect that purists will be unhappy at my sacrificing the precision of strict nomenclature and stereochemical descriptors in my attempt to keep the text as simple as possible. To any offended parties, I apologise. No doubt I will be hearing from you.

The book is structured along the lines of reaction types, and important methods for achieving asymmetric synthesis in the particular reaction type are presented in each individual chapter. I have attempted to make each chapter on reaction types stand alone, with the references presented at the end of each chapter. This inevitably leads to some repetition both in the text and references, but I hope that this makes the book easier to use.

Given the timescale involved, it is inevitable that this book cannot be an up-to-the-minute account of the art of asymmetric synthesis, and I am conscious that much progress has been made during the time in which it has been written. I am also conscious of the fact that I have had to choose examples from a literature which is rich with outstanding achievements. I am lucky enough to be able to count some of the leading exponents in asymmetric synthesis amongst my friends, and to them and all other researchers in the area, I apologise for the inevitable omission of many fine examples of the art. Again, no doubt I will be hearing from you!

This book has taken a long time to write, and I am indebted to the patience of all who have been involved with it, especially the editorial staff at Oxford University Press. A good part of the text and references have been read and commented on by a number of students at Salford, and particular thanks go to Adrian Gill. I should be grateful to hear of the errors which will inevitably have crept into this book, in spite of the best efforts of all involved. As I have typed the text, drawn the diagrams, and

'typeset' the book myself, I bear all the blame for such errors. No doubt I shall be hearing about them.

Finally, I could not finish this without thanking my family, especially Mandy, for putting up with the 'unsocial hours' which I have had to keep at times during the writing and preparation of the manuscript.

Salford
1995

Garry Procter

To Mandy, Adam, and Rachel

Contents

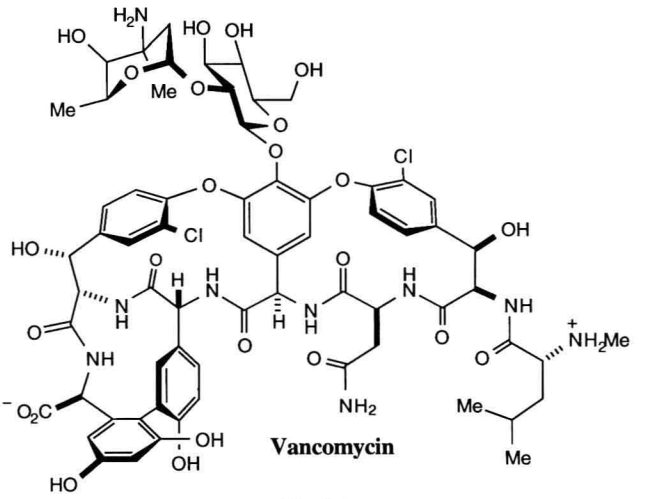
1 Introduction

Organic compounds play an important part in modern life, not least in the area of pharmaceuticals, agrochemicals, and other materials which possess useful biological activity. Often such biological activity arises through the interaction of the organic compound with a 'biomolecule' such as an enzyme or a receptor. Such sites of action are constructed from chiral building blocks such as amino acids or carbohydrates, which means that these sites of action are themselves chiral. Being natural chiral compounds, these building blocks are present as single enantiomers, and it follows of course that the resulting biomolecules are single enantiomers. If the organic compound itself is chiral, then one consequence of this is that the two enantiomers are likely to interact differently with a given biomolecule of the type described above. In general, when considering the interaction of two such chiral systems, the stereochemistry of both systems can have a profound effect on the magnitude of the interaction, and therefore on the biological response.

This principle can be illustrated by considering the natural antibiotic vancomycin. Vancomycin is an orally active antibiotic which is widely used in treatment of postoperative diarrhoea, and is a heptapeptide with the absolute stereochemistry shown in Fig. 1.1.[1]

The molecular basis for its mode of action has been shown to involve its binding to cell-wall mucopeptide precursors terminating in the sequence -D-Ala-D-Ala (Fig. 1.2). As might be expected from this mode of action, vancomycin will bind to the model dipeptide PhCO-D-Ala-D-Ala (**1.1**).

Changing the stereochemistry of the terminal alanine residue in the model (**1.2**) causes a decrease in binding energy of 10 kJ mol^{-1}. This means that



Vancomycin

Fig. 1.1

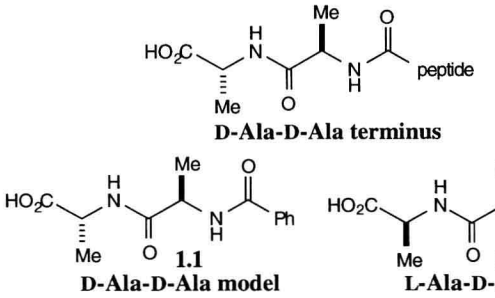


Fig. 1.2

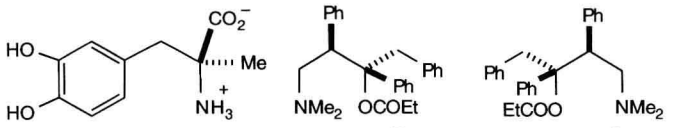
vancomycin can 'discriminate' between a D- and an L-amino acid at the terminus of the dipeptide as a result of this difference in binding energy. The binding constant for the model with the natural stereochemistry is fifty times greater than that for the model with the unnatural stereochemistry. For the related antibiotic ristocetin, the corresponding ratio of binding constants is between five hundred and four thousand to one.

As stated earlier, if a pharmaceutical, or any biologically active compound, is chiral then the enantiomers are likely to interact differently with the natural biomolecule. The enantiomers will probably possess different levels of biological activity, and could also exhibit quite different types of activity. In effect, the two enantiomers should be viewed as two distinct compounds. It follows that using the racemate of a particular biologically active compound is equivalent to using a mixture of two different compounds.[2]

Usually, one enantiomer is far more active than the other. This being the case it is clearly undesirable to use a racemic biologically active compound. Only one of the enantiomers possesses the desired beneficial activity, but *both* enantiomers carry the risk of undesirable activity (side-effects). Moreover, the possible side-effects could be different for each enantiomer. For the active enantiomer the risk of side-effects is far outweighed by the positive effect, otherwise the material would be of little use. The inactive enantiomer provides little or no benefit, but does carry the risk. In addition, the enantiomers are likely to be metabolized either at different rates or by different pathways, as the enzymes which perform the metabolism are themselves chiral.

For a chiral biologically active compound the following possibilities exist:
(1) only one of the enantiomers is active, the other being devoid of activity;
(2) both enantiomers are active, but they have very different potencies;
(3) both enantiomers have similar or equal activities;
(4) both enantiomers are active, but the type of activity is different.

It is common for either situation (1) or (2) to prevail. For example, in the case of the hypertensive agent α-methyldopa, all the activity resides in the L-enantiomer (Fig. 1.3).[3] It is relatively rare for both enantiomers to have similar potency, but examples are known, as they are for the case in which the enantiomers have different activities. Propoxyphene is interesting in that both



L-α-Methyldopa **Darvon®** **Novrad®**

Fig. 1.3

enantiomers have useful but different biological activities. The D-enantiomer is an analgesic, whereas the antipode possesses antitussive properties but no analgesic effect. To reflect the mirror image relationship between these two compounds, they have been given the trade names Darvon® and Novrad® (Fig. 1.3).[4]

The obvious solution to the potential problems related to the use of a racemate is to use only the enantiomer which possesses the desired beneficial biological activity. An equally obvious prerequisite for this general solution is that the pure single enantiomers be available. Two possible methods for achieving this are immediately apparent: resolution of the racemate or an intermediate on the synthetic route, and the use of an enantiomerically pure starting material. Both these are valuable methods, and are currently in use, but both have associated drawbacks as general solutions. Resolution is often expensive as a suitable resolving agent is required and the unwanted enantiomer has to be disposed of. The use of an enantiomerically pure starting material requires that such a compound be readily available, possesses the desired absolute configuration, and that a convenient and practical synthetic route to the desired compound can be developed.

In principle, a general solution to the problem of obtaining enantiomerically pure organic compounds would be to have available an array of synthetic methods which result in the desired transformation *and* control the absolute stereochemistry of chiral centres which are created as a result of the synthetic operation. This is the realm of asymmetric synthesis.

At present, there are relatively few enantioselective synthetic methods which come up to the high standards which would bring them into everyday use and allow for the cost-effective preparation of enantiomerically pure compounds on a reasonable scale.[5] Organic chemists are fortunate in that this area is full of challenges which make scientific demands at the highest level, and that success in this area can have immediate application in the chemical industry. Developing solutions to these challenges involves working at the leading edge of the subject in a highly creative manner. The rest of this volume is concerned with some of the more important methods for asymmetric synthesis and the principles which lie behind them.

References

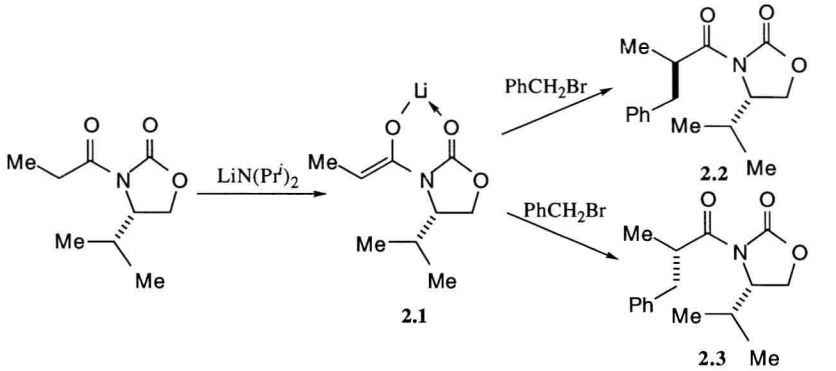
1. This discussion of vancomycin is based on Williams, D. H., Doig, A. J., Cox, J. P. L., Nicholls, I. A., and Gardener, M. (1990), in *Chirality in Drug Design and Synthesis*, (ed. C. Brown), pp. 101–113, Academic Press, London, and references cited therein.
2. For a discussion of this and related problems, see Ariens, E. J. (1990), in *Chirality in Drug Design and Synthesis*, (ed. C. Brown), pp. 29–43, Academic Press, London.
3. Gillespie, L., Oates, J. A., Crout, J. R., and Sjoerdsma, H. (1962), *Circulation*, **25**, 281.
4. Drayer, D. E. (1986), *Clin. Pharmacol. Ther.*, **40**, 125.
5. For a discussion of the industrial synthesis of single enantiomers, see Sheldon, R. (1990), *Chem. and Ind.*, 212.

2 Principles

In order to achieve asymmetric synthesis, at least one component of the reaction must be chiral and non-racemic. If there is no asymmetric component in the reaction, then transition states which lead to enantiomers will themselves be enantiomeric, equal in energy, and a racemate must be formed. In principle, the use of a chiral, non-racemic substrate, reagent, solvent, or catalyst should lead to asymmetric synthesis. In general terms, *any* feature of the reacting system which would cause the possible transition states for the reaction to be *diastereoisomeric* (where they would normally be *enantiomeric*) could lead to the preferential formation of one diastereoisomer or enantiomer. This follows because transition states which are diastereoisomeric need not be of the same energy and consequently one of the possible products could be formed more rapidly. The various possibilities will be considered in this chapter.

If the substrate itself is chiral and non-racemic, then creation of another chiral centre using this substrate provides the possibility of diastereoisomeric products. If the products themselves are diastereoisomers, then the transition states which lead to them are diastereoisomeric, and a diastereoselective reaction should be expected.

This principle is illustrated in Fig. 2.1, which shows the two possible paths for alkylation of the chiral enolate **2.1**. The use of this type of chiral enolate for asymmetric synthesis will be covered in detail later. If the electrophile attacks from above the plane of the enolate as drawn, the product will be **2.2**, and attack from below will lead to **2.3**, which is diastereoisomeric with **2.2**. In this case the ratio of **2.2**:**2.3** is 99:1, often expressed as a diastereoisomeric excess (Fig. 2.1).[1] This particular reaction is an example of an extremely powerful method for asymmetric synthesis based on the use of 'chiral auxiliary' controlled enolate alkylation.



Diastereoisomeric excess (d.e.)= major diastereoisomer (%) – %minor diastereoisomer (%)
= **2.2**(%) – **2.3**(%) = 99 – 1 = 98%

Fig. 2.1

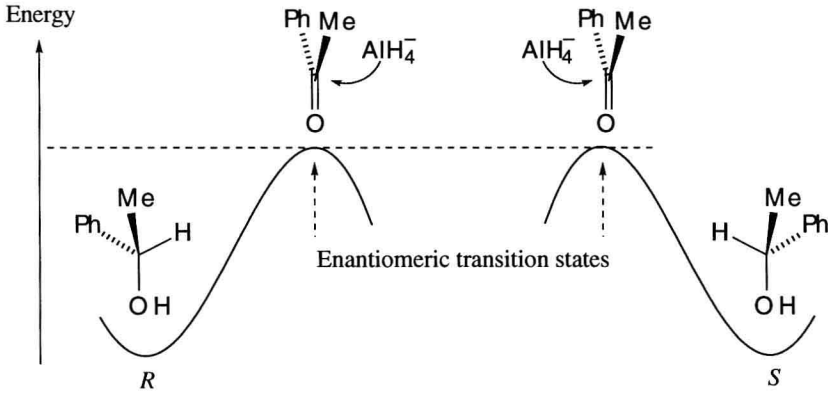
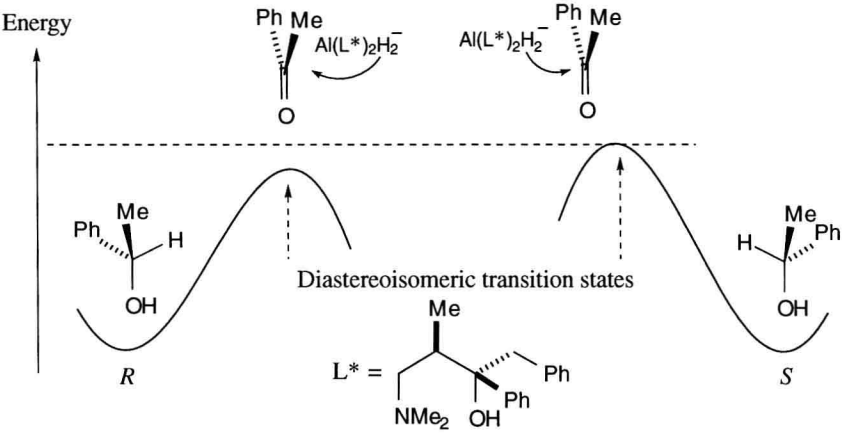


Fig. 2.2

The use of a chiral, non-racemic reagent may be understood by considering the reduction of a prochiral ketone to the corresponding chiral alcohol using either an achiral or a chiral reducing agent. For the achiral reagent, reduction *must* give a racemic mixture since the two transition states are enantiomeric and therefore of equal energy. Clearly this must lead to equal amounts of each enantiomer as the rates of both reactions will be the same (Fig. 2.2).

If a chiral, non-racemic reducing agent is used, because this is involved in the transition states these become diastereoisomeric and need not be of the same energy. The reaction will then produce an excess of the enantiomer which is formed via the lower energy transition state (Fig 2.3).

The example shown in Fig. 2.3 involves the prior reaction of the achiral reducing agent ($LiAlH_4$) with the enantiomerically pure 1,3-aminoalcohol



Enantiomeric excess (e.e.) = major enantiomer(%) - minor enantiomer(%)
= *R*(%) - *S*(%) = 68%

Fig. 2.3

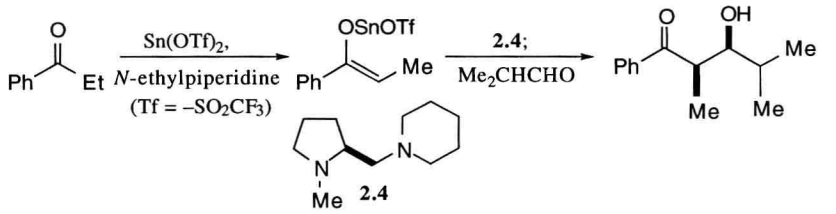


Fig. 2.4

shown (commonly known as 'Darvon alcohol') which produces a chiral, non-racemic complex represented as $Al(L^*)_2H_2$. Using this as the reducing agent results in the transition states which had previously been enantiomeric (Fig. 2.2) becoming diastereoisomeric and therefore of different energies. Transition states *enantiomeric* with those represented in Fig. 2.3 would require the *enantiomer* of the 1,3-aminoalcohol, which is not present as enantiomerically pure 1,3-aminoalcohol was used. In this particular case the enantiomeric excess of the product is 68 per cent, in favour of the (*R*)-alcohol.[2]

The components of a reaction which takes place in solution will be solvated. Consequently, the use of a solvent which is chiral and non-racemic should lead to asymmetric synthesis as the solvent is likely to be involved in the transition states. As only one enantiomer of the solvent is present, transition states which would be enantiomeric in an achiral solvent become diastereoisomeric and asymmetric synthesis becomes possible. In spite of the attractive nature of this approach to asymmetric synthesis it is currently of little general use, as the level of stereoselectivity induced is often low and unpredictable. Moreover, there are very few enantiomerically pure compounds which are available in sufficient quantity and which possess the properties required to be a useful solvent.

Rather more promising is the use of chiral, non-racemic solvating agents (in a normal solvent) which preferentially solvate a reaction component. Fig. 2.4 shows an example of this type of asymmetric synthesis in which a tin(II) enolate is complexed with a chiral, non-racemic diamine **2.4** before reaction with the aldehyde. The product is obtained in 75 per cent enantiomeric excess.[3]

A chiral, non-racemic catalyst can be used for asymmetric synthesis and the principles of this approach can be understood using arguments similar to those

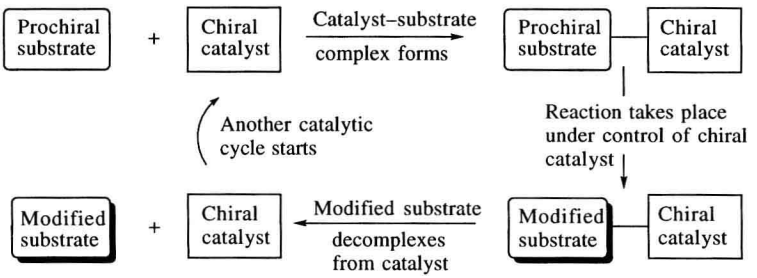


Fig. 2.5

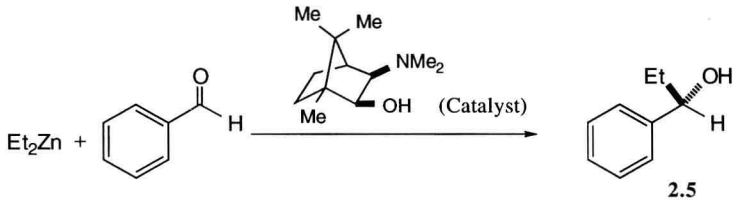


Fig. 2.6

above. In this case the stoichiometric reagent is achiral but does not react with the prochiral substrate in the absence of the catalyst. The reaction in which the new chiral centre is created only occurs when the catalyst brings together the reagent and substrate. The catalyst is involved in the transition states and it follows that these will be diastereoisomeric, which should lead to asymmetric synthesis. A schematic representation of such asymmetric catalysis is shown in Fig. 2.5.

This type of asymmetric synthesis is extremely attractive, as a small amount of the chiral, non-racemic catalyst leads to stoichiometric amounts of the desired enantiomerically enriched product. Indeed this type of asymmetric synthesis is widespread; Nature uses chiral, non-racemic catalysts (enzymes) to carry out many enantioselective (and diastereoselective) reactions. In the laboratory and in industry both enzymes and synthetic catalysts are used to achieve asymmetric synthesis. Examples of asymmetric catalysis will be discussed where appropriate, and one such is illustrated in Fig. 2.6. The product alcohol **2.5** is formed in 97 per cent yield and 98 per cent enantiomeric excess.[4]

Another general approach to asymmetric synthesis involves the use of chiral auxiliaries. The overall strategy is shown in Fig. 2.7 and has clear similarities with the asymmetric catalysis cycle shown in Fig. 2.5. In this approach the prochiral substrate is attached to a chiral, non-racemic group, known as the chiral auxiliary, prior to reaction. The two (or more) possible products then become diastereoisomeric and one should be formed in excess. The major diastereoisomer can then be isolated and the chiral auxiliary removed to provide the chiral non-racemic product. The requirements for a chiral auxiliary to be practically useful are listed in Table 2.1, and at present there are relatively few

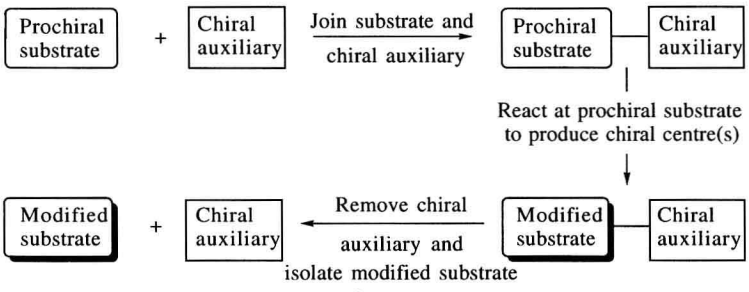


Fig. 2.7

Table 2.1 Requirements for chiral auxiliaries

Enantiomerically pure
Cheap and easy to obtain in quantity
Easy to attach to substrate
Control of stereoselectivity high and predictable
Easy to purify major diastereoisomer
Removal easy without loss of diastereoisomeric or enantiomeric purity
Easily separated from product and recovered

chiral auxiliaries which meet all these demands.

The oxazolidinone chiral auxiliaries introduced at the beginning of this chapter (Fig. 2.1) provide an excellent example of what can be achieved using chiral auxiliaries, and will be discussed in detail in Chapters 4, 5, and 6. A simple example which uses the alkylation reaction shown in Fig. 2.1 is given below (Fig. 2.8).

An alternative approach to asymmetric synthesis is that of kinetic resolution, in which a resolution of a racemic substrate is achieved at the same time as an asymmetric reaction. This approach relies on the difference in the rate of reaction of the individual enantiomers of the racemate with an enantiomerically pure reactant, reagent, or catalyst. In an ideal case this rate difference is so large that one enantiomer of the racemate is effectively inert, while the other reacts rapidly. Routine separation of the product and the unreacted enantiomer would then provide both in an enantiomerically pure form. An example of kinetic resolution using the Sharpless asymmetric epoxidation (discussed in Chapter 7) is shown in Fig. 2.9.

The examples considered so far have involved reactions in which only one of the components is chiral. Only the stereoselectivity induced by this component

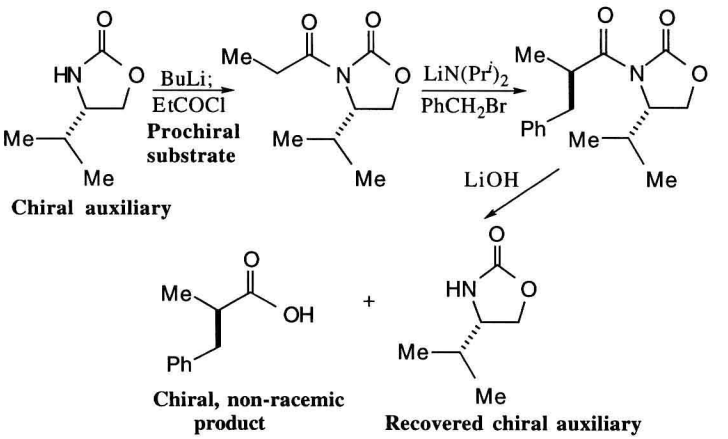


Fig. 2.8

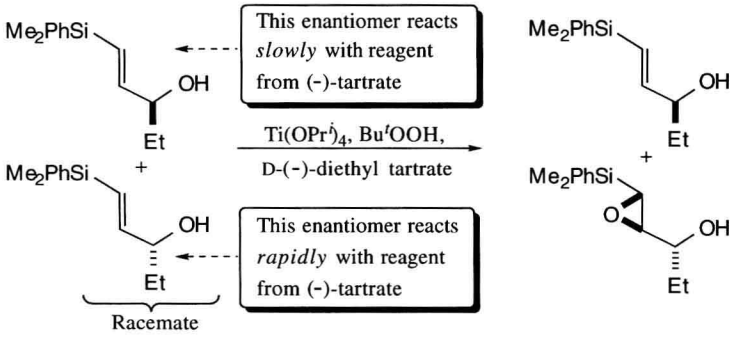


Fig. 2.9

needs to be considered. For a reaction in which two components are chiral then the 'intrinsic stereoselectivity' of each is important. To illustrate the possibilities when two chiral components are used, two extreme cases will be considered.

In the simplest of these, the 'intrinsic' reaction stereoselectivity of one of the components dominates the reaction. In this case the absolute configuration of the new chiral centre(s) is independent of the chirality of the other component. This is often the case in reactions of the oxazolidinone chiral auxiliaries discussed above. The aldol reaction of **2.6** (Fig. 2.10) with the chiral aldehyde **2.7** provides **2.8** with a selectivity of >400:1,[5] in this case the stereoselectivity of the enolate far outweighs the intrinsic diastereoselectivity of the aldehyde.

At the other extreme the two chiral components have similar intrinsic diastereoselectivities. In this case the diastereoselectivities of one pair of chiral components will usually be complementary and will give high stereoselectivity. This combination is often known as the *matched pair*. The other combination will usually result in low stereoselectivity and is often referred to as the *mismatched pair*. This general approach is known by several terms, including 'double asymmetric synthesis'[6] and 'double asymmetric induction', and is more easily understood by considering an example (Fig. 2.11).

Fig. 2.11 illustrates the application of double asymmetric synthesis to a Diels–Alder reaction.[7] The intrinsic diastereoselectivity of the diene **2.9** is estimated by its reaction with an achiral dienophile **2.10** (Reaction 1) and that

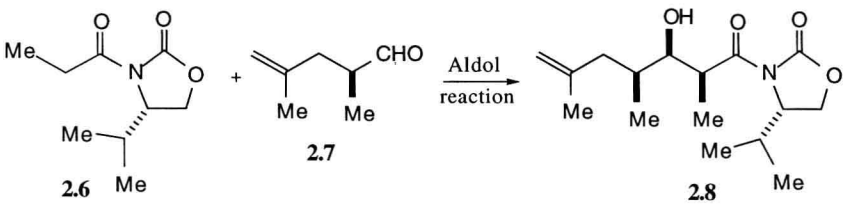


Fig. 2.10