KINETIC RESOLUTION STRATEGIES

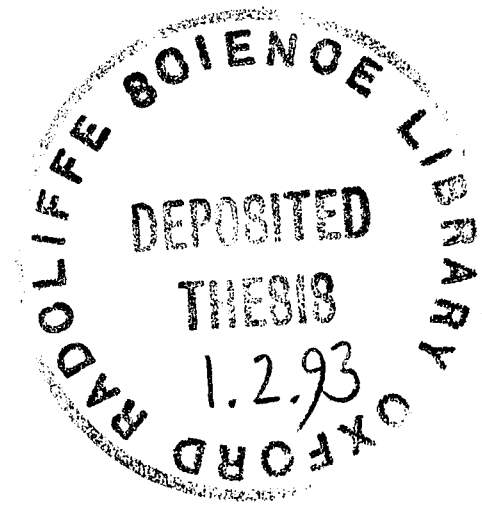
A thesis submitted in partial fulfilment

of the requirements for the degree of

Doctor of Philosophy

by

J. A. A. de Sousa, B.Sc. (Hons)



New College

Oxford

November 1992

Kinetic Resolution Strategies

J. A. A. de Sousa
New College, Oxford

D. Phil.
November 1992

Abstract

This thesis is concerned with the use of kinetic resolution strategies for the preparation of enantiomerically pure materials.

Chapter 1 introduces kinetic resolution. The limitations of conventional kinetic resolutions are described and the methods used to overcome these limitations are discussed.

Chapter 2 presents a double kinetic resolution strategy where the recovered reactant from the first kinetic resolution is used as starting material in a second kinetic resolution. In the second kinetic resolution the major enantiomer present in the starting material is the faster reacting enantiomer. Application of this double kinetic resolution strategy to the Sharpless epoxidation is shown to enable enhanced product enantiomeric excesses to be obtained.

Chapter 3 presents an alternative double kinetic resolution strategy where the product from the first kinetic resolution is used as starting material in a second kinetic resolution. In the second kinetic resolution the major enantiomer present in the starting material is the faster reacting enantiomer. Application of this double kinetic resolution strategy using lipase mediated esterification and hydrolysis reactions is shown to enable enhanced product yields to be obtained.

Chapter 4 describes the preparation of an enantiomerically pure 2-substituted mono-protected propan-1,3-diol derivative *via* combination of an asymmetric synthesis and a kinetic resolution.

Chapter 5 describes the preparation of the pheromone sulcatol in enantiomerically pure form *via* combination of an asymmetric synthesis and a kinetic resolution.

Chapter 6 presents an investigation into the structure of lithium(α-methylbenzyl)-benzyl amide.

Chapter 7 describes an attempted dynamic kinetic resolution of 2-substituted mono-protected propan-1,3-diol derivatives.

Chapter 8 describes an attempted preparation of the iron crotonyl complex E-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=$CHCH_3$)] in enantiomerically pure form *via* enzymic kinetic resolution.

Acknowledgements

Firstly, I would like to thank my supervisor Dr. Steve Davies for his advice and support over the last three years.

I am grateful to ICI (Fine Chemicals Manufacturing Organisation) for their financial support and to my industrial supervisor Dr. Steve Brown for his interest in my work.

Many thanks are due to the technical staff at the Dyson Perrins Laboratory, in particular Elizabeth McGuinness, Tina Jackson, Val Lamburn, Robin Procter and Dr. Robin Aplin.

I am greatly indebted to my many proof readers: Kevin Fitzpatrick, David White, Dr. Steve Case-Green, Iain Walters, Dr. Michael Metzler, Dr. Guy Krippner, Jonathan Bryden, Paul de Sousa and Anne de Sousa.

I thank, in addition to those already mentioned above, Dr. Peter Stephenson, Dr. Robert Polywka, Dr. Narciso Martín Garrido, Osamu Ichihara, Dr. Andrew Mortlock and Doreen Shirley for making the lab. a more bearable place in which to work and for many useful discussions.

I thank my family for their endless love, support and encouragement and for giving me every opportunity.

Finally, I thank Anne for making everything worthwhile.

Contents

Abbreviations

B*, B†	homochiral catalyst or reagent
c	conversion
de	diastereomeric excess
ee	enantiomeric excess
E	stereoselectvity factor or enantiomeric ratio
k	specific rate constant
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutyl aluminium hydride
DiPT	diisopropyl tartrate
DMF	dimethylformamide
DMAE	N,N-dimethylaminoethanol
DMAP	4-dimethylaminopyridine
DNBOH	dinitrobenzoic acid
hfc	3-(heptafluoropropylhydroxymethylene)camphorato
HMPA	hexamethylphosphoramide
LDA	lithium diiisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidine
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
PPTS	pyridinium *p*-toluenesulphonate
py	pyridine
TBHP	*t*-butylhydroperoxide
THF	tetrahydrofuran
Me	CH_3
Et	CH_2CH_3
Pr	$CH_2CH_2CH_3$
iPr	$CH(CH_3)_2$
Bu	$CH_2CH_2CH_2CH_3$
iBu	$CH_2CH(CH_3)_2$
tBu	$C(CH_3)_3$
Ph	phenyl

Bn	CH_2Ph
Np	1-naphthyl
BOM	CH_2OCH_2Ph
MOM	CH_2OCH_3
Ac	acetyl
c-C_6H_{11}	cyclohexyl
(η^5-C_5H_5)	(η^5-cyclopentadienyl)
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TMS	trimethylsilyl
ANL	*Aspergillus niger* lipase
CCL	*Candida cylindracea* lipase
LL	lipoprotein lipase from *pseudomonas* sp.
MJL	*Mucor javanicus* lipase
PFL	*Pseudomonas fluorescens* lipase
PLE	pig liver esterase
PPL	pig pancreatic lipase
RAL	*Rhizopus arrhizus* lipase
ΣIII	lipase from *pseudomonas* sp. type XIII
sp.	species
GLC	gas liquid chromatography
HPLC	high performance liquid chromatography
TLC	thin layer chromatography
NMR	nuclear magnetic resonance
s	singlet
d	doublet
t	triplet
q	quartet
sx	sextet
m	multiplet
br	broad
m/z	mass/charge ratio
s	strong
vs	very strong

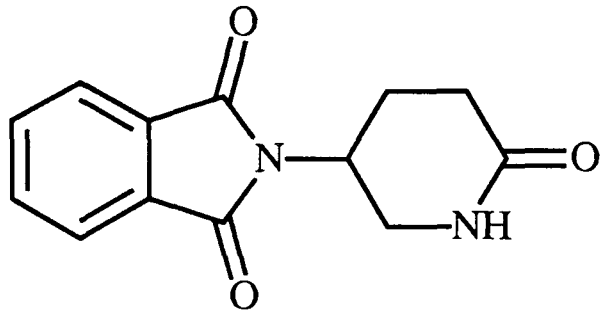
Chapter 1

Introduction to Kinetic Resolution.

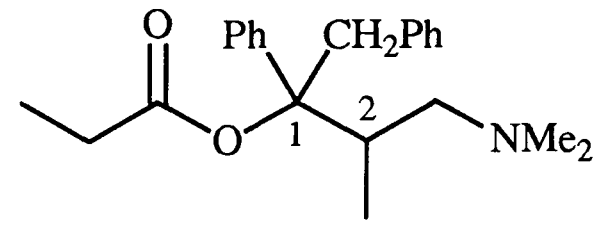
1.1 The Importance of Chirality.

In those cases where a biologically active compound contains one or more stereogenic centres, the desired biological activity is often only caused by one of the enantiomerically and diastereomerically pure stereoisomers. In the best cases the other stereoisomers have no effect. Unfortunately, it has often been found that the other stereoisomers can inhibit the desired effect or even give rise to undesirable side effects.[1] The most widely documented example of this phenomenon is the drug thalidomide (**1**) which was administered as a racemate. It was subsequently found that only *(R)*-**1** has the desired anti-emetic properties whereas *(S)*-**1** exhibits teratogenic activity (**Figure 1**).[2] Another example is the drug propoxyphene (**2**): *(1R,2S)*-**2** has been found to have analgesic properties whereas *(1S,2R)*-**2** has anti-tussive properties (**Figure 1**).[3]

Figure 1 : Activity of the enantiomers of thalidomide (**1**) and propoxyphene (**2**).



(R)-**1** : anti-emetic
(S)-**1** : teratogen



(1R,2S)-**2** : analgesic
(1S,2R)-**2** : anti-tussive

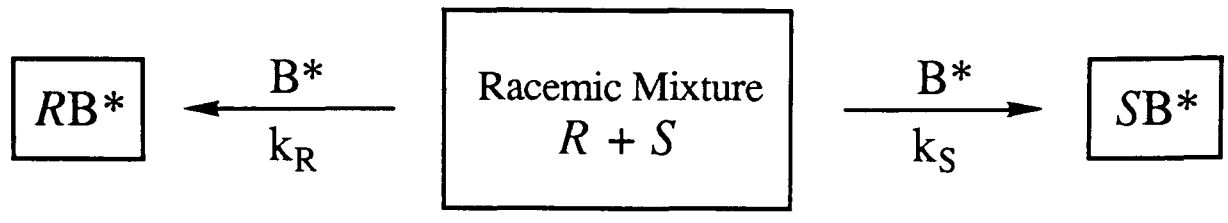
The increasing awareness of the importance of chirality to biological activity has led to great interest in the preparation of homochiral (enantiomerically pure) materials.[4]

1.2 Kinetic Resolution.[5]

A number of different methods have been employed for the preparation of homochiral materials.[6] One method that has been widely used is kinetic resolution.

Kinetic resolution is defined as a process in which one of the enantiomers of a racemic mixture is more readily transformed to product than the other enantiomer. In order for this to occur the reaction must be mediated by a homochiral catalyst or reagent (**Scheme 1**).

Scheme 1 : Kinetic resolution.



k_R and k_S = specific rate constants for reaction of *R* and *S* respectively.
B* is a homochiral catalyst or reagent.

If $k_R \neq k_S$, and the reaction is stopped at some point between 0 and 100% conversion, the process can be described as a kinetic resolution. The difference in specific rate constants arises because reaction of the enantiomers with the homochiral catalyst or reagent proceeds *via* two diastereomeric transition states. Being diastereomeric the transition states may have different energies, in which case the rate of reaction of each enantiomer will be different.

For chemical processes, the ratio of specific rate constants is defined as the stereoselectivity factor (E) and is an indication of how efficient a kinetic resolution process is.[5a] Mathematical relationships (**Figure 2**) have been derived that relate the stereoselectivity factor with the enantiomeric excess of recovered reactant (ee_R); enantiomeric excess of the product (ee_P) and the extent of reaction (c). These relationships allow easy calculation of the stereoselectivity factor for all kinetic resolutions where the reaction is first order with respect to the reactant; any order with respect to the homochiral catalyst or reagent and irreversible.[7] The same relationships can also be applied to biochemical kinetic resolutions, although in these cases E is the ratio of specificity constants and is often described in the chemical literature as the "enantiomeric ratio".[7a] For clarity, throughout this thesis E is referred to as the stereoselectivity factor for both chemical and biochemical kinetic resolutions.

Figure 2 : Mathematical relationships used for the calculation of stereoselectivity factors.

$$E_R = \frac{\ln[(1-c)(1-ee_R)]}{\ln[(1-c)(1+ee_R)]}$$

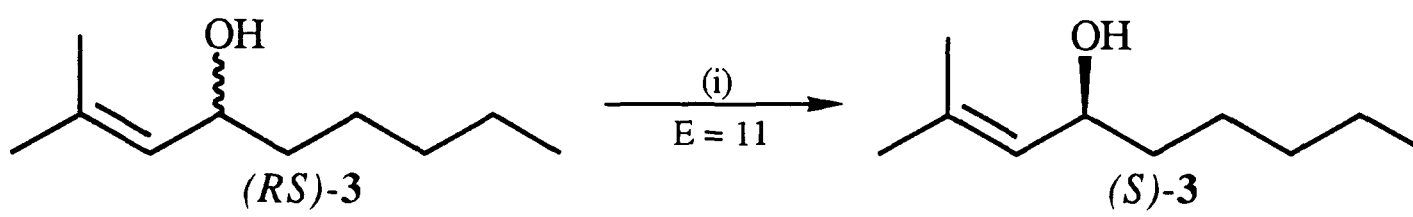
E_R = stereoselectivity factor calculated with respect to reactant.

$$E_P = \frac{\ln[1-c(1+ee_P)]}{\ln[1-c(1-ee_P)]}$$

E_P = stereoselectivity factor calculated with respect to product.

Recent examples of kinetic resolution include the reduction of a number of allylic alcohols using the $Ru(BINAP)(OAc)_2$ catalyst. As shown in **Scheme 2**, 2-methyl-2-nonen-4-ol (**3**) (at 100 atmospheres of hydrogen) is reduced with a stereoselectivity factor of 11.[8]

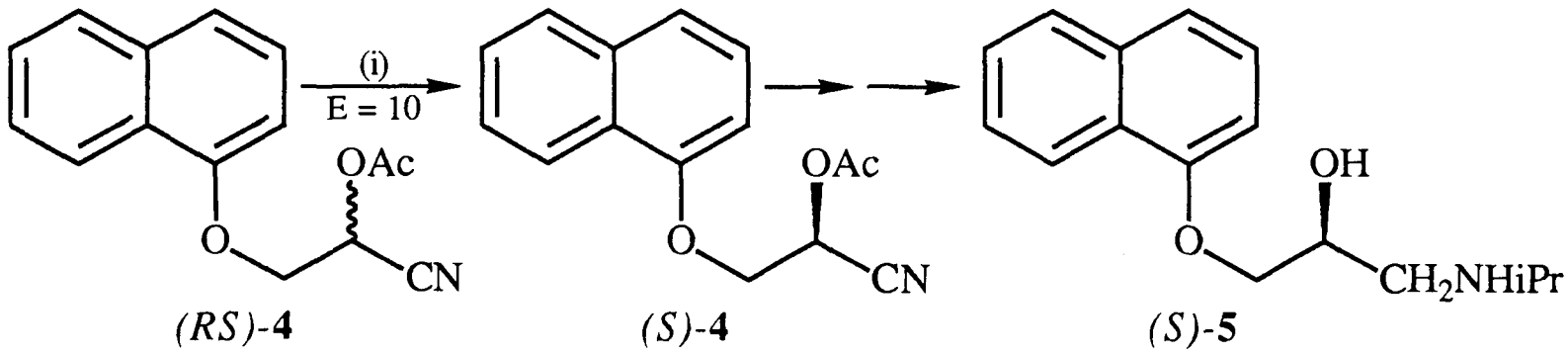
Scheme 2 : Kinetic resolution *via* $Ru(BINAP)(OAc)_2$ catalysed hydrogenation.



(i) Ru[*(S)*-BINAP]$(OAc)_2$, 100 atm H_2.

Enzymic kinetic resolution of the racemic cyanohydrin acetate (**4**) using the lipase from *pseudomonas* sp. was found to proceed with a stereoselectivity factor of 10. The recovered reactant was transformed in two steps to the β-blocker *(S)*-propranolol (**5**) (**Scheme 3**).[9]

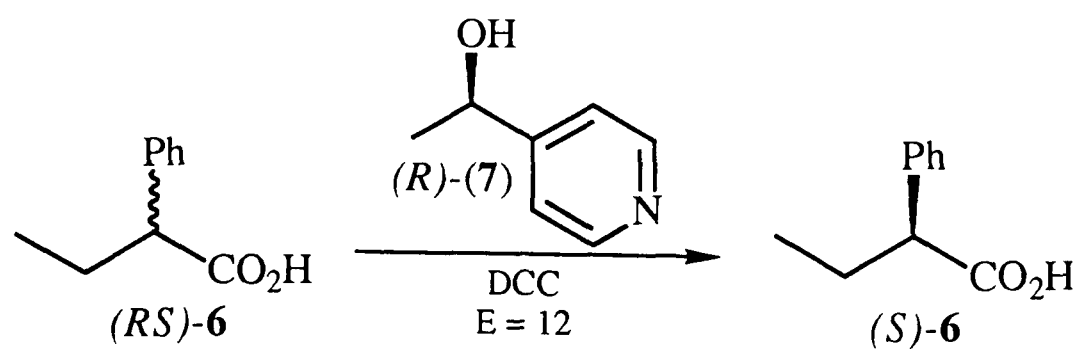
Scheme 3 : Use of kinetic resolution in the preparation of *(S)*-propranolol (**5**).



(i) Lipase from *pseudomonas* sp., pH 5.

Another example is the kinetic resolution of racemic phenylbutanoic acid (**6**) using *(R)*-1-(4-pyridyl)ethanol (**7**). In this case a stereoselectivity factor of 12 was observed (**Scheme 4**).[10]

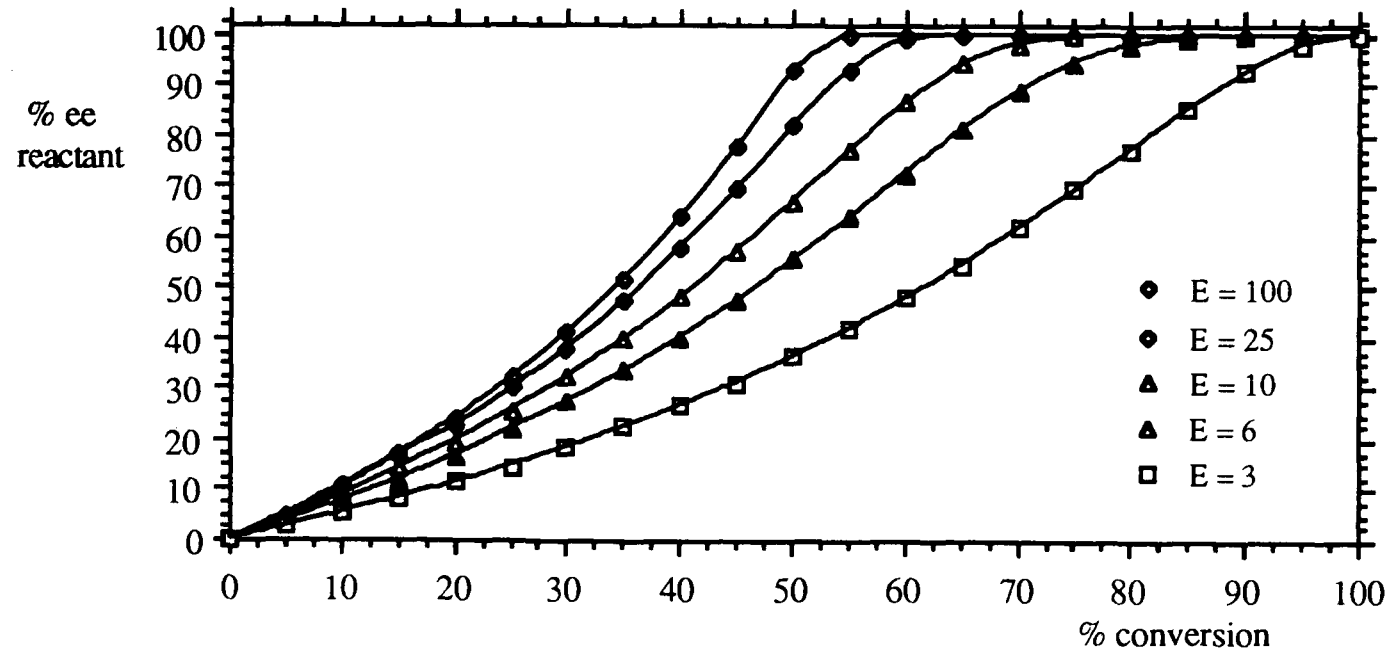
Scheme 4 : Kinetic resolution of phenylbutanoic acid (**6**) using 1-(4-pyridyl)ethanol (**7**).



1.3 Limitations of Conventional Kinetic Resolution.

The fundamental limitation of conventional kinetic resolution is mass action: the concentration of the slower reacting enantiomer increases relative to that of the faster reacting enantiomer so that the difference in their rates of reaction is continuously diminishing. Therefore as a kinetic resolution proceeds, the starting material is increasingly enriched in the slower reacting enantiomer. The product is enriched in the faster reacting enantiomer and its enantiomeric excess drops as the kinetic resolution proceeds. This is shown graphically in **Figures 3** and **4** for a range of stereoselectivity factors.

Figure 3 : % Enantiomeric excess of reactant vs % conversion for kinetic resolutions with various stereoselectivity factors.



As can be seen from **Figure 3**, even when E is small the reactant can be obtained with high enantiomeric excesses (albeit at the expense of yield), simply by allowing the resolution to proceed to high conversions. According to Sheldon, in order to be economically attractive to the chemical industry, only kinetic resolutions with stereoselectivity factors of at least 20 are capable of yielding sufficient quantities of recovered reactant with suitably high enantiomeric excesses.[4a]

Ideally, E should be very large so that essentially only one enantiomer of the starting material reacts. If this were the case the reaction would stop when 50% of the starting material had been consumed and the material recovered would consist of homochiral starting material and homochiral product.

Figure 4 : % Enantiomeric excess of product vs % conversion for kinetic resolutions with various stereoselectivity factors.

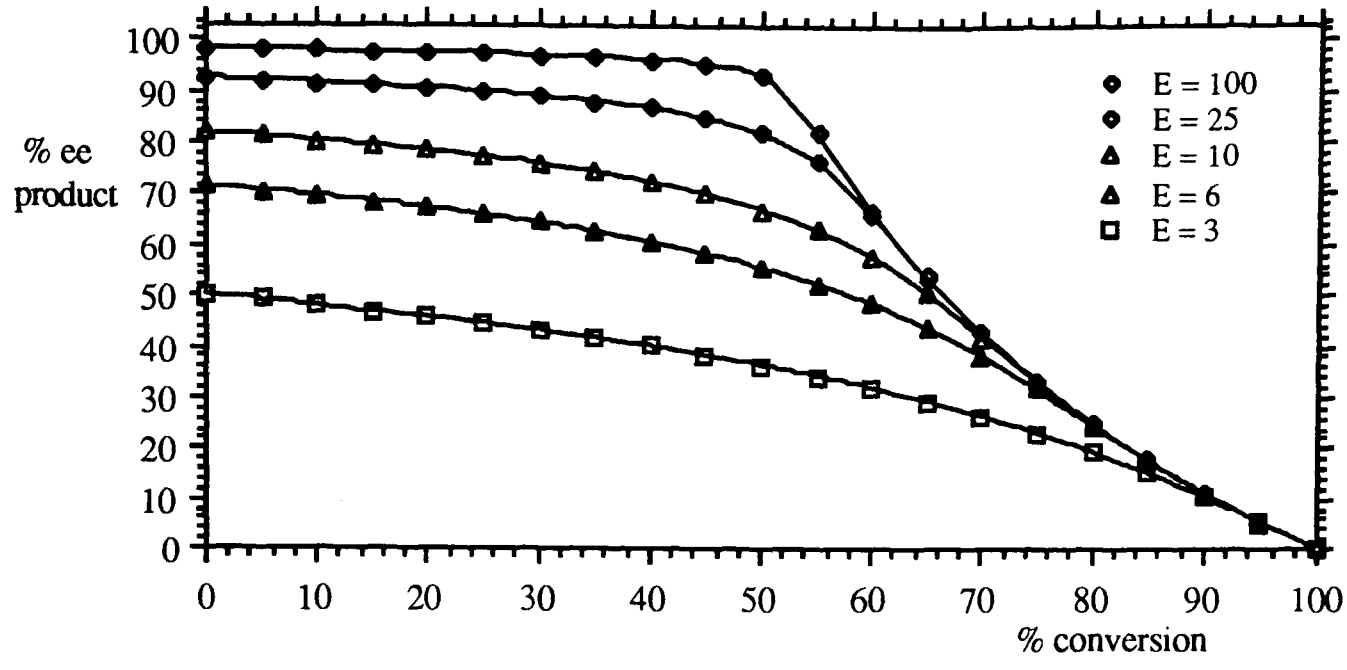


Figure 4 shows that the product from a kinetic resolution can only be obtained with high enantiomeric excesses when E is large (>50). Maximum product enantiomeric excess is obtained at an infinitesimally small conversion and can be calculated using the relationship: maximum ee_P = (E-1)/(E+1). For example when E = 10, maximum enantiomeric excess of product = 81.8%.

Due to the small number of kinetic resolutions where E is large, practical applications of kinetic resolution have largely been restricted to the preparation of the reactant, with little attention having been paid to the product of the kinetic resolution.

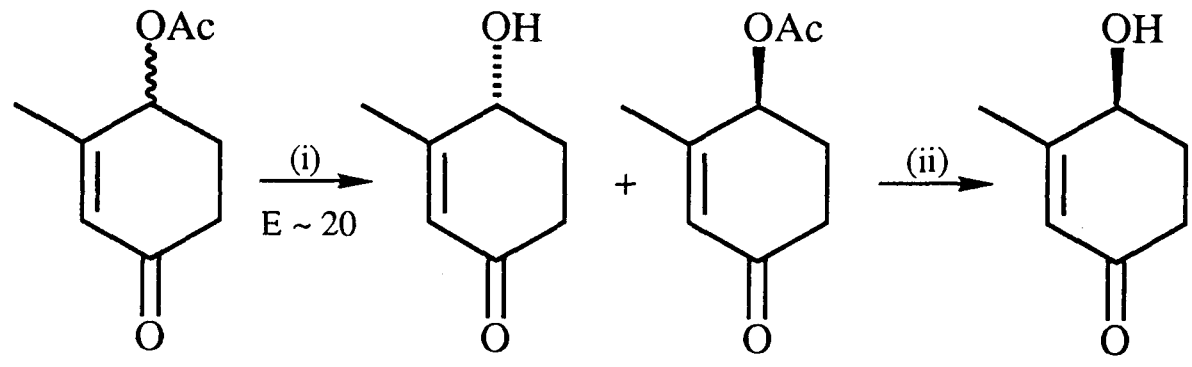
1.4 Methods used to Overcome the Limitations of Conventional Kinetic Resolutions.

As detailed above, one of the major limitations of conventional kinetic resolutions is the fact that high product enantiomeric excesses can only be obtained for kinetic resolutions that have high stereoselectivity factors. For example (using the relationship mentioned previously), to obtain any product with an enantiomeric excess of 95%, E must be at least 39. Similarly, for a product enantiomeric excess of 99%, E must be at least 199. Examples of kinetic resolutions in the literature with stereoselectivity factors as high as this are very rare. Consequently, a number of methods have evolved that enable high product enantiomeric excesses to be obtained by the use of kinetic resolutions with more modest stereoselectivity factors.

1.4.1 Conversion of the Recovered Reactant to the Desired Product.

As mentioned before (see **Figure 3**), the recovered reactant from a kinetic resolution can be obtained with high enantiomeric excess simply by allowing the kinetic resolution to proceed to high conversion. Thus, the simplest method for obtaining product with high enantiomeric excess is to run the kinetic resolution to the conversion at which the reactant has the required enantiomeric excess, and then (after isolation) transform the recovered reactant to the required product.[11] This method was used by Frejd *et al.* for the preparation of *(S)*-4-hydroxy-3-methyl-2-cyclohexenone (**9**) as shown in **Scheme 5**.[11a] The kinetic resolution proceeds with E ~ 20 and therefore in this case, the maximum product enantiomeric excess (which would be obtained at an infinitesimally small conversion) is 90%. However, the required product (**9**) was obtained with 99% enantiomeric excess by the simple non-selective hydrolysis of the recovered reactant (**8**) to give the desired product (**9**).

Scheme 5 : Preparation of *(S)*-4-hydroxy-3-methyl-2-cyclohexenone (**9**).



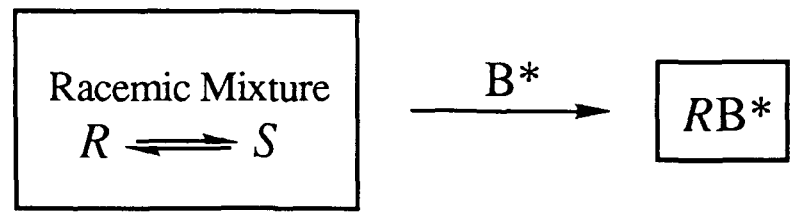
(i) Pig liver esterase, pH 7. 62% conversion.
(ii) Na_2CO_3/MeOH.

1.4.2 Dynamic or Second Order Kinetic Resolution.

As stated previously, the maximum theoretical yield of a pure enantiomer obtainable by conventional kinetic resolution procedures is 50%. A dynamic[12] or second order[13] kinetic resolution process is capable of producing a pure enantiomer with a theoretical yield of 100%. In a dynamic kinetic resolution (**Scheme 6**) the enantiomers of the reactant readily interconvert in the reaction medium, and at the same time a homochiral reagent or catalyst (B*) preferentially transforms one enantiomer of the

reactant into product. If the stereoselectivity factor is large, high product enantiomeric excesses may be obtained.

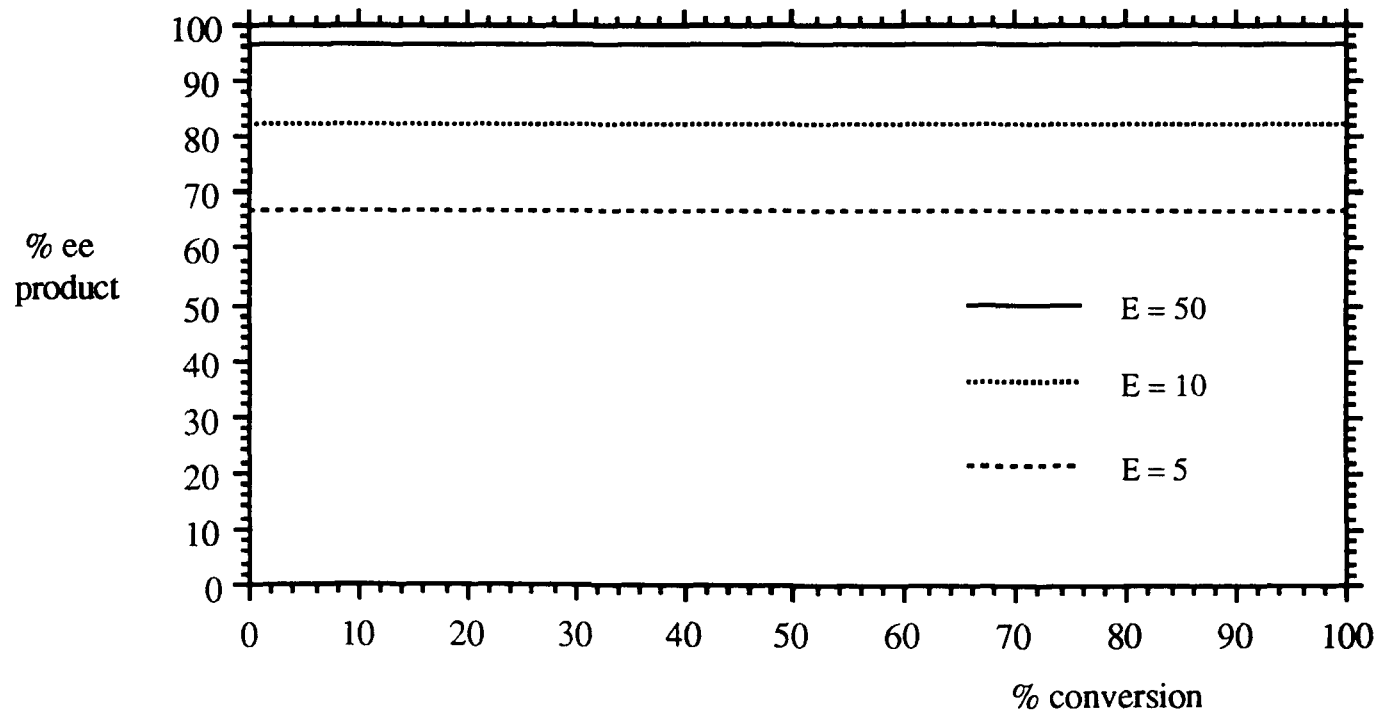
Scheme 6 : Dynamic or second order kinetic resolution.



B* is a homochiral catalyst or reagent.

If the rate of racemisation is significantly greater than the rate of asymmetric transformation, there will be no mass action effect as the starting material will appear to be racemic at all times. This means that, instead of decreasing as the kinetic resolution proceeds (as with conventional kinetic resolution), the enantiomeric excess of the product is independent of the extent of reaction as shown in **Figure 5**.

Figure 5 : % Enantiomeric excess of product vs % conversion for dynamic kinetic resolutions with various stereoselectivity factors.

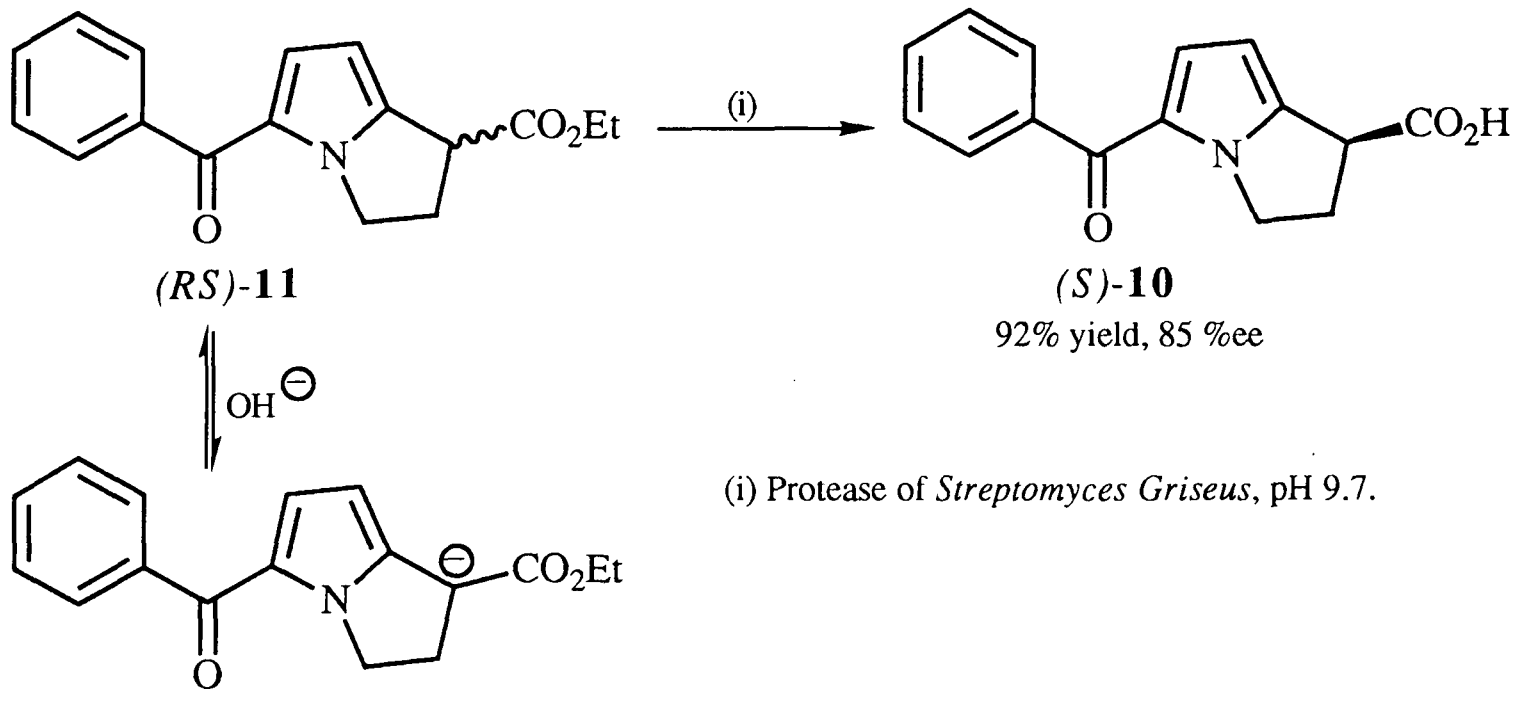


There are a number of difficulties in designing systems for dynamic kinetic resolution. Firstly, the reaction medium must racemise only the reactant; the product and the homochiral catalyst or reagent must be left stereochemically uncorrupted. Secondly, since it is the product that is required, high enantiomeric excesses are only available for

asymmetric reactions that proceed with a high stereoselectivity factor (E). For example when E = 10, product enantiomeric excess will be 82%; when E = 50, product enantiomeric excess will be 96%. The rate of racemisation must also be significantly faster than the rate of the asymmetric transformation reaction. Finally, any "racemising agent" used must be compatible with the homochiral reagent or catalyst. The paucity of examples of dynamic kinetic resolution that appear in the chemical literature illustrates the extent of these challenges.[14]

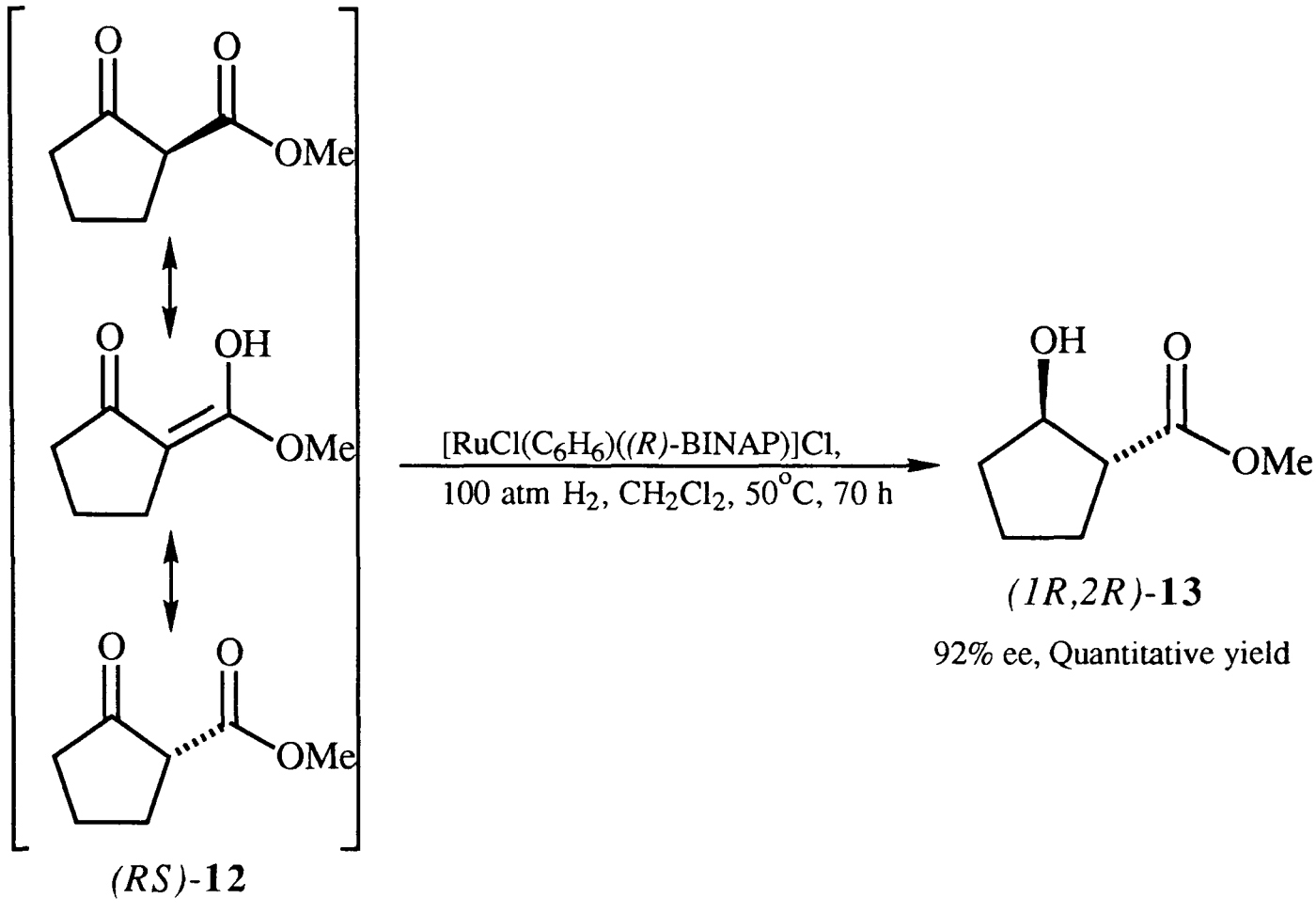
Sih *et al.* used a dynamic kinetic resolution to prepare the potent anti-inflammatory agent and analgesic ketrolac (**10**).[15] Enzymic hydrolysis of the ethyl ester of ketrolac (**11**), under mildly basic conditions, leads to formation of the required *(S)*-ketrolac (**10**) in 92% yield and with an enantiomeric excess of 85%. Racemisation of the reactant is brought about by formation of the resonance stabilised enolate of the ethyl ester (**11**) as shown in **Scheme 7**.

Scheme 7 : Dynamic kinetic resolution in the preparation of *(S)*-ketrolac (**10**).



Noyori *et al.* performed a dynamic kinetic resolution on a number of 2-substituted-3-oxo carboxylic acid esters. In the example shown in **Scheme 8** the racemic cyclic ketone (**12**) is hydrogenated in the presence of a homochiral ruthenium BINAP catalyst to form the *trans*-hydroxy ester (**13**) in quantitative yield and with an enantiomeric excess of 92%.[12]

Scheme 8 : Stereoselective hydrogenation *via* dynamic kinetic resolution.



(RS)-**12**

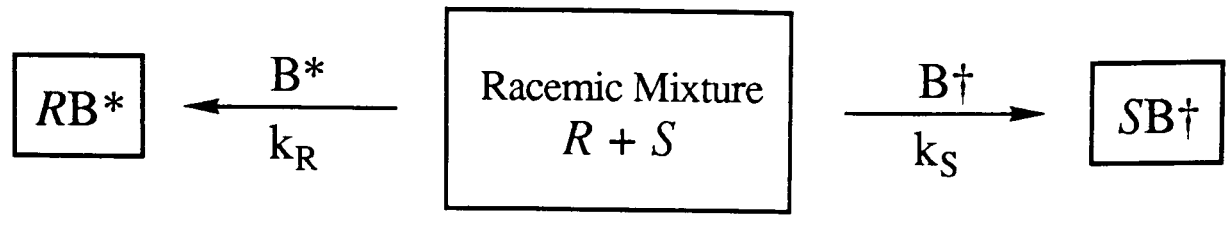
(1R,2R)-**13**

92% ee, Quantitative yield

1.4.3 Simultaneous Kinetic Resolution.

Simultaneous kinetic resolution exploits a similar principle to dynamic kinetic resolution: the mass action effect, that occurs in conventional kinetic resolution and which causes the enantiomeric excess of the product to decrease as the conversion increases, is negated. With simultaneous kinetic resolution, two homochiral catalysts or reagents (B* and B†) are used synchronously (**Scheme 9**). One of the homochiral reagents (in this case B*) reacts preferentially with the *R* enantiomer of the reactant and the other homochiral reagent (in this case B†) reacts preferentially with the *S* enantiomer. Provided that the rate of each reaction is identical, and that they both display the same (but opposite) degree of stereoselectivity, the reactant will remain racemic. This implies that the enantiomeric excess (or diasteromeric excess) of the products (*R*B* and *S*B†) are independent of conversion and are governed solely by the stereoselectivity factors of the two reactions. When all of the reactant has been consumed, the two chemically different products should be separable by normal methods.[16]

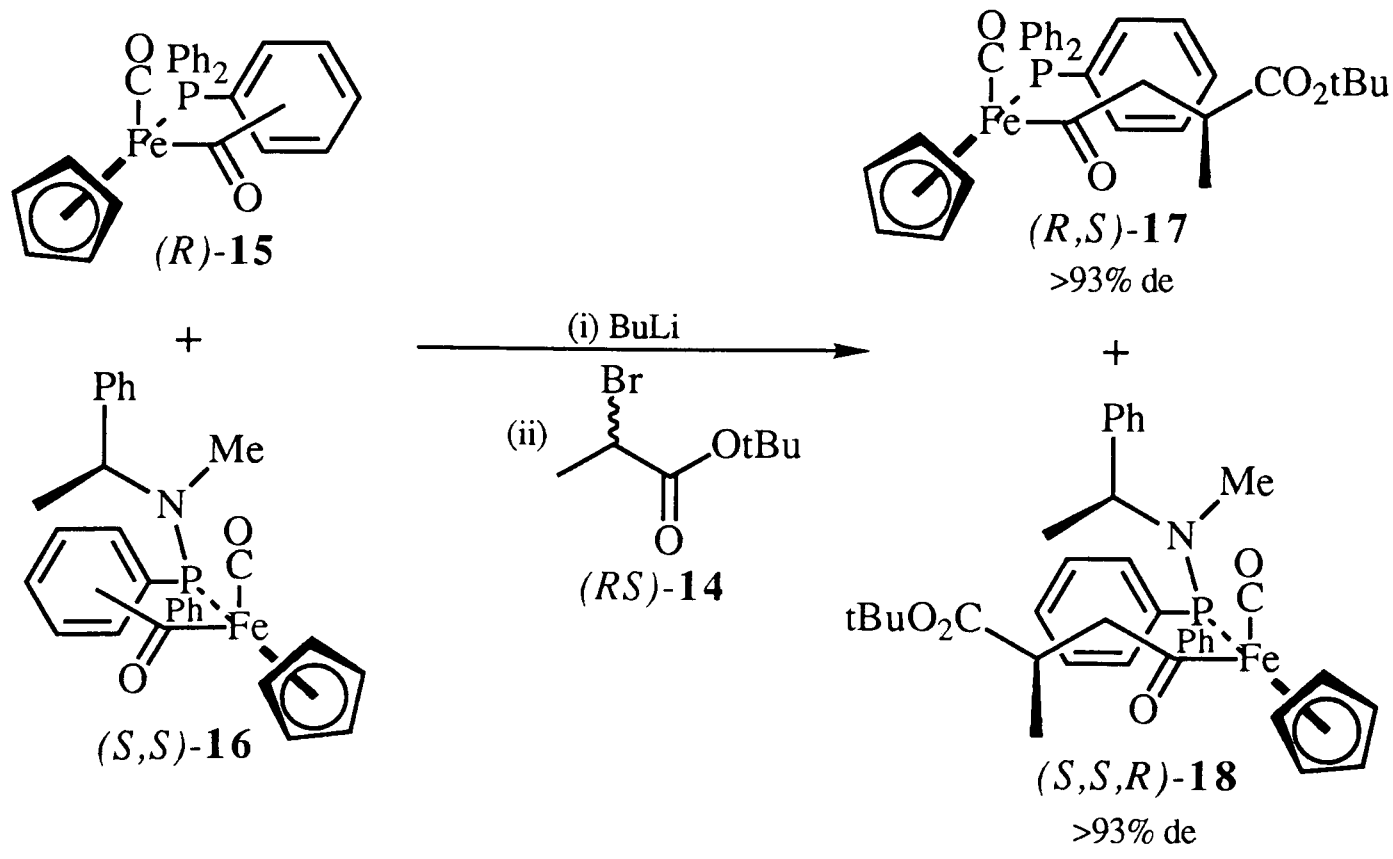
Scheme 9 : Simultaneous kinetic resolution.



k_R and k_S = specific rate constants for reaction of *R* and *S* respectively.
B* and B† are non-enantiomeric homochiral catalysts or reagents.

One example of this type of process uses *t*-butyl-2-bromopropanoate (**14**) as the reactant and the iron acyl complexes* *(R)*-**15** and *(S,S)*-**16** as the two homochiral reagents.[18] It was found that *(R)*-**15** reacted preferentially with *(S)*-*t*-butyl-2-bromopropanoate (**14**) to give *(R,S)*-**17**, whereas *(S,S)*-**16** reacted preferentially with *(R)*-*t*-butyl-2-bromopropanoate (**14**) to give *(S,S,R)*-**18**. Both products were formed with diastereomeric excesses of > 93% (**Scheme 10**).

Scheme 10 : Simultaneous kinetic resolution using homochiral iron complexes.



* Ligand priority for iron complexes has been assigned as C_5H_5 > PPh_3 > CO > acyl. The relative configuration of the stereogenic centres is given starting with and in increasing distance from the iron atom.[17]

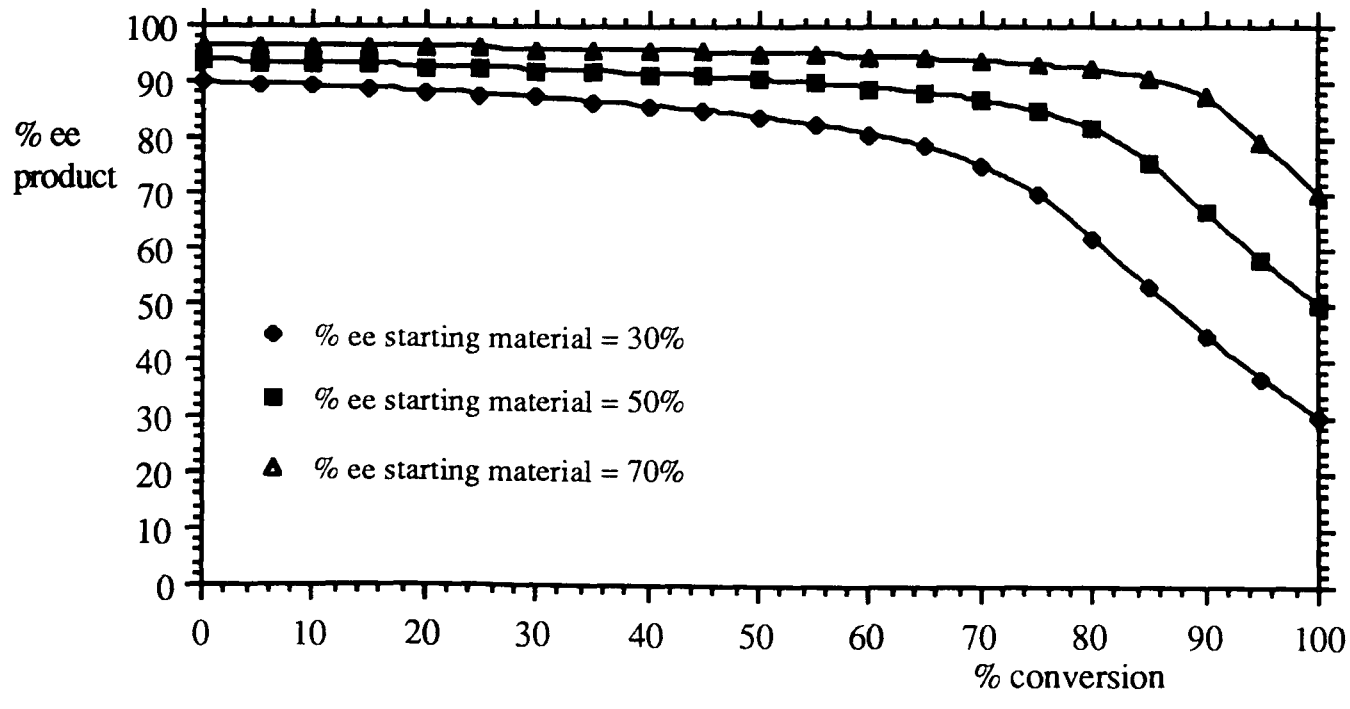
1.4.4 Sequential Kinetic Resolution.

Combinations of more than one kinetic resolution have been found to be successful in enabling the formation of materials with enhanced enantiomeric excesses or yields when compared with those obtainable using conventional kinetic resolution processes. As described below, a number of different methods for combining kinetic resolutions have been used.

1.4.4.1 Recycling of the Product.

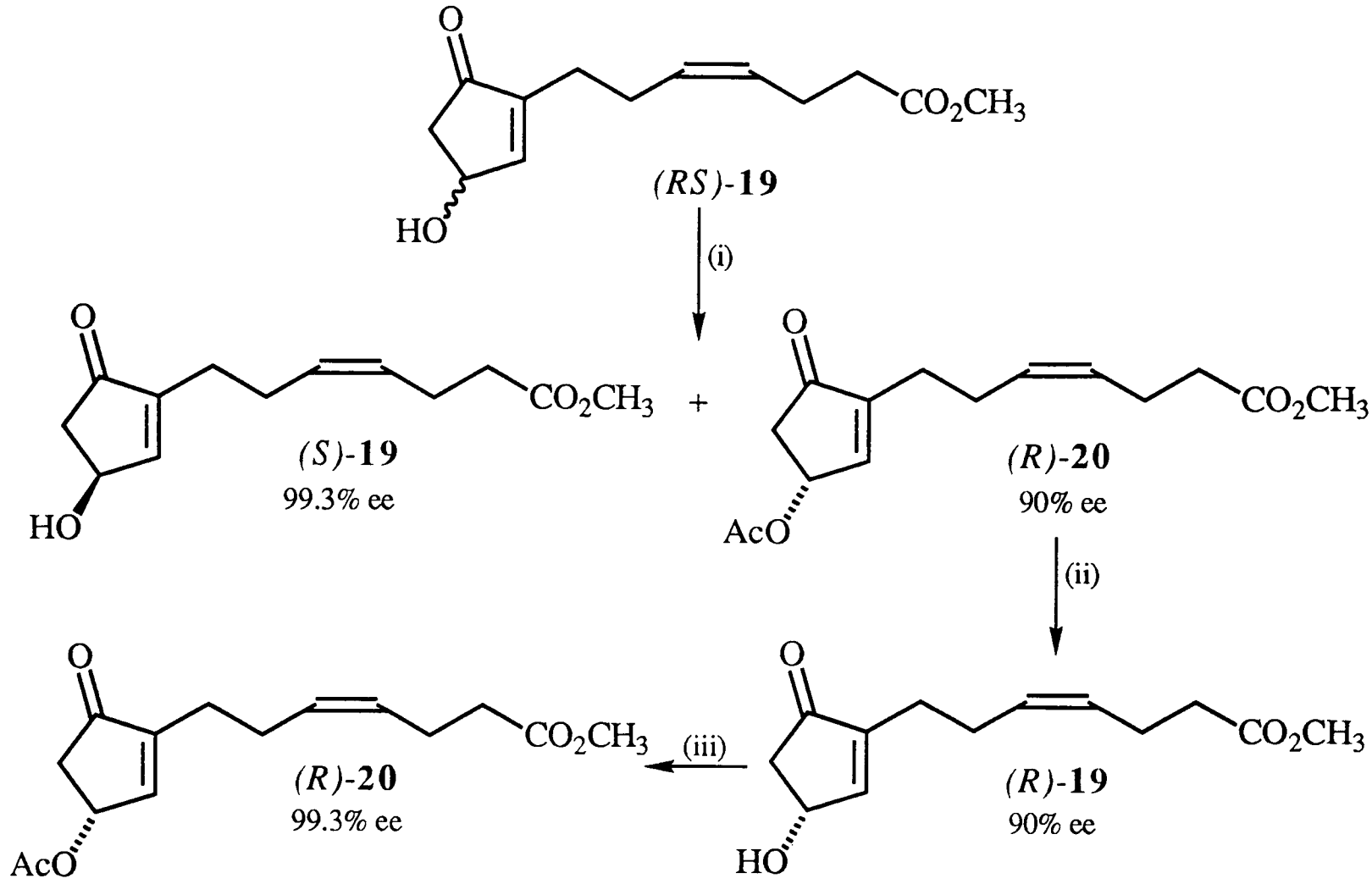
One method that has been used to obtain enhanced product enantiomeric excesses from kinetic resolutions with low stereoselectivity factors involves recycling the product. If the product from the initial kinetic resolution is converted back to the reactant and then a second kinetic resolution (using the same system) is performed on this scalemic starting material, it allows formation of products with higher enantiomeric excesses (**Figure 6**). In principle the process can be repeated a number of times until the required product enantiomeric excess is obtained.

Figure 6 : % Enantiomeric excess of product vs % conversion for kinetic resolution (E = 10) of a scalemic starting material (where the major enantiomer is faster reacting).



This methodology has been implemented on a number occasions.[19] For example, Babiak *et al.* prepared the prostaglandin precursor (**19**) as shown in **Scheme 11**.[20]

Scheme 11 : Use of product recycling in kinetic resolution.



(i) PPL, vinyl acetate. 52% conversion.
(ii) Guanidine, MeOH.
(iii) PPL, vinyl acetate. 91% conversion.

In the first kinetic resolution (**Scheme 11**) the pig pancreatic lipase (PPL) mediated acetylation was stopped at ~ 52% conversion. This gave rise to recovered reactant [*(S)*-**19**] with >99.3% enantiomeric excess and product [*(R)*-**20**] with 90% enantiomeric excess. Hydrolysis of *(R)*-**20** using guanidine in methanol gave *(R)*-**19**, which was then used as the reactant for the second kinetic resolution (using the same enzymic system). This time the reaction was halted after ~ 91% conversion giving rise to product [*(R)*-**20**] with >99.3% enantiomeric excess.

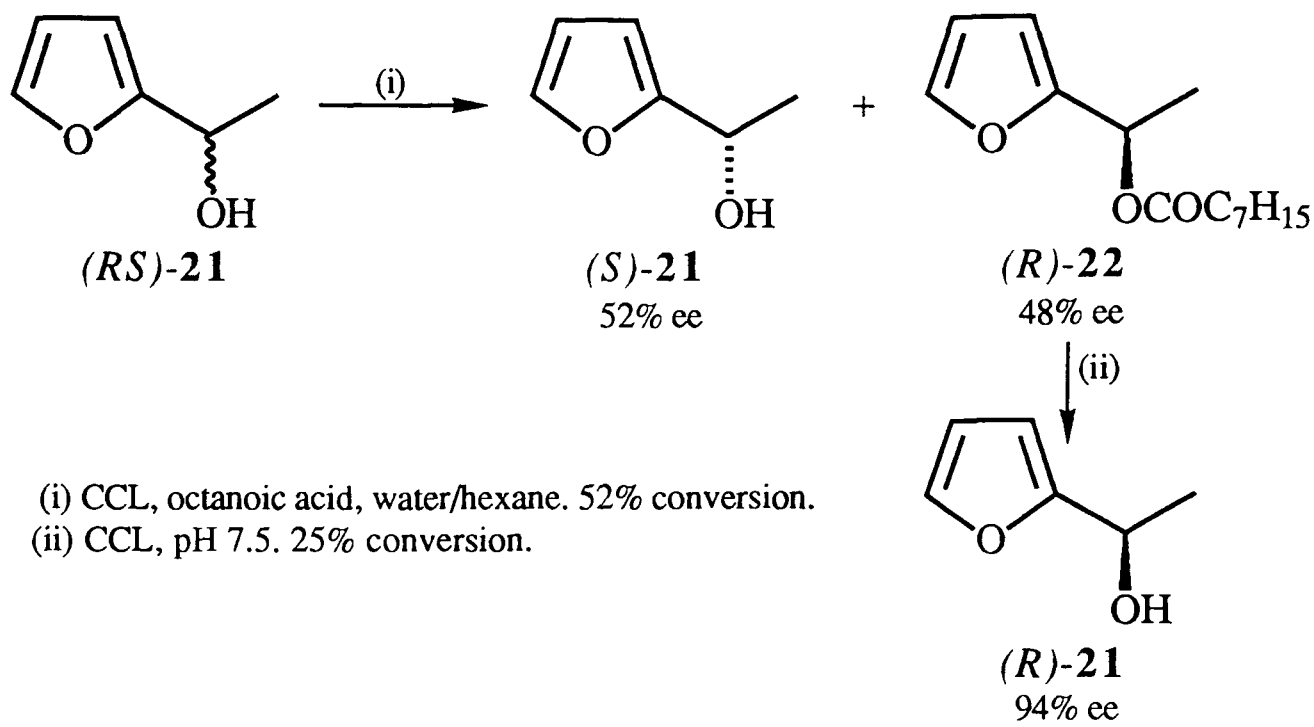
This recycling approach can be used for any kinetic resolution, provided that the product can easily be transformed back to the reactant.

1.4.4.2 Use of the Product from the First Kinetic Resolution as Starting Material in a Second Kinetic Resolution in which the Major Enantiomer is the faster reacting.

Examples have appeared recently (see Chapter 3) where instead of converting the product from the first kinetic resolution back to the reactant and then performing the second kinetic resolution (as described in Section 1.4.4.1), a different kinetic resolution system is used in the second step. In this strategy the scalemic product (from the first kinetic resolution) is used directly as the starting material in the second kinetic resolution. This section describes processes such as this where in the second kinetic resolution, the major enantiomer (present in the starting material) is the faster reacting enantiomer. This means that the product (rather than the recovered reactant) from the second kinetic resolution can be obtained with higher enantiomeric excess.[21] Variation of % enantiomeric excess of the product from the second kinetic resolution with % conversion is identical to that for the recycling strategy described in Section 1.4.4.1 (**Figure 6**). However, this strategy has an advantage over recycling in that there is one less step involved, although obviously, it does require that a suitable second kinetic resolution system be available.

When this project started, the only example in the chemical literature where this methodology had been used was that reported by Wong *et al.* for the synthesis of *(R)*-furylmethylcarbinol (**21**).[22] Firstly, *candida cylindracea* lipase (CCL) mediated enzymic esterification was performed and gave recovered reactant *(S)*-**21** with 52% enantiomeric excess and the product ester *(R)*-**22** with ~ 48% enantiomeric excess. In the second kinetic resolution, CCL mediated hydrolysis of *(R)*-**22** (48% ee) led to formation of *(R)*-**21** with an enantiomeric excess of 94% (**Scheme 12**).

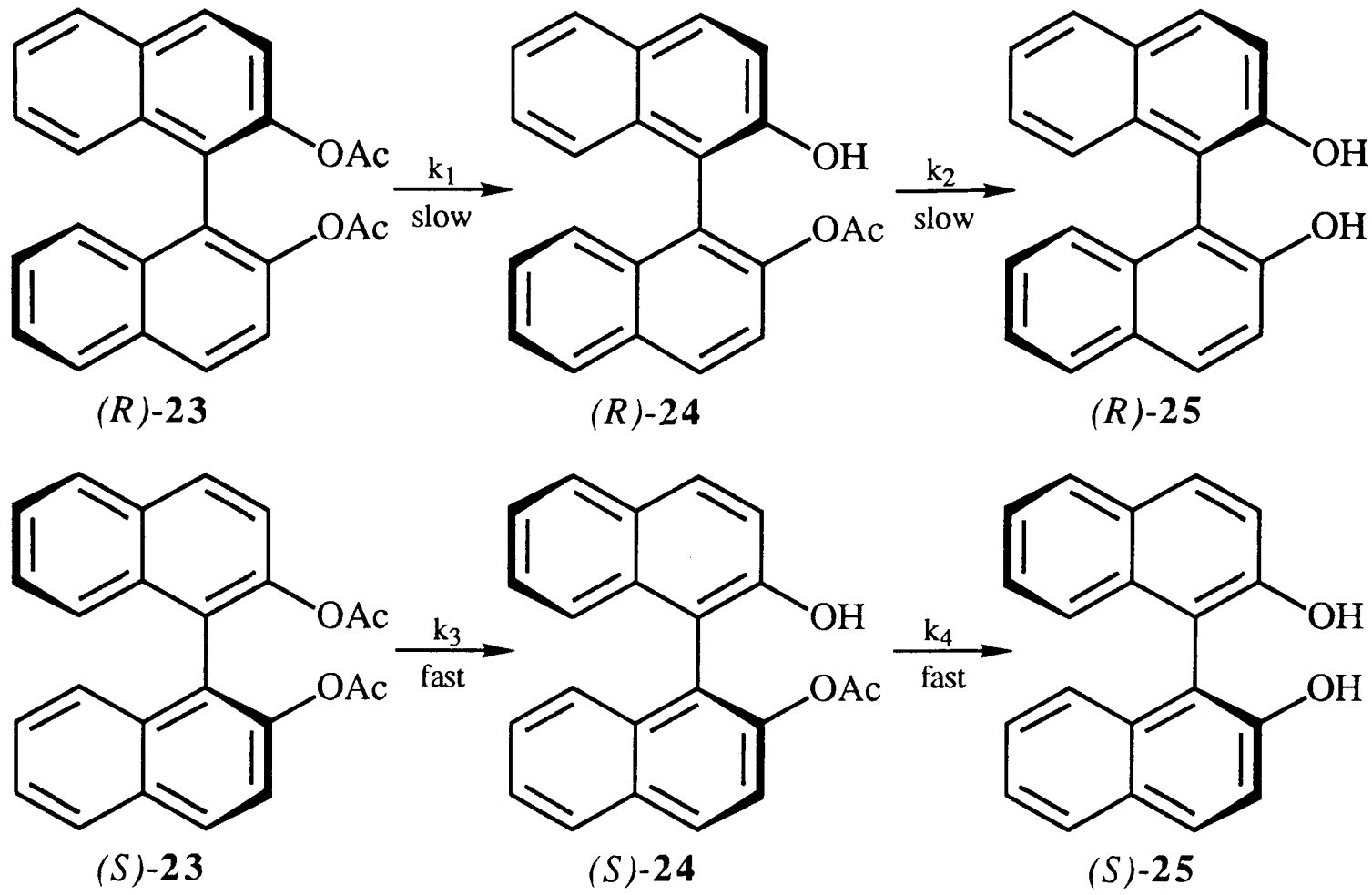
Scheme 12 : Alternative method for product recycling.



(i) CCL, octanoic acid, water/hexane. 52% conversion.
(ii) CCL, pH 7.5. 25% conversion.

The most efficient examples of this process are those in which the two kinetic resolutions proceed in the same reaction medium (as this negates the need to stop the first kinetic resolution, isolate the product and perform the second kinetic resolution separately). Once again, there were very few examples of this type of process in the chemical literature,[23] however a number have recently appeared.[24] The earliest example was the enzymic hydrolysis of *(RS)*-diacetoxy binaphthol (**23**) using *absidia glauca* as shown in **Scheme 13**.[23a] Examination of the reported relative rate constants (k_n in **Scheme 13**) for each step shows that in the first step, the *S* enantiomer of the racemic diacetate (**23**) is preferentially hydrolysed to the monoacetate [*(S)*-**24**]. In the second step, the *S* enantiomer of **24** is the faster reacting enantiomer and is preferentially hydrolysed to *(S)*-binaphthol (**25**). Stopping the reaction at ~ 50% conversion gave *(S)*-**25** with an enantiomeric excess of 90%.

Scheme 13 : Enzymic kinetic resolution of *(RS)*-**23** using *absidia glauca.*



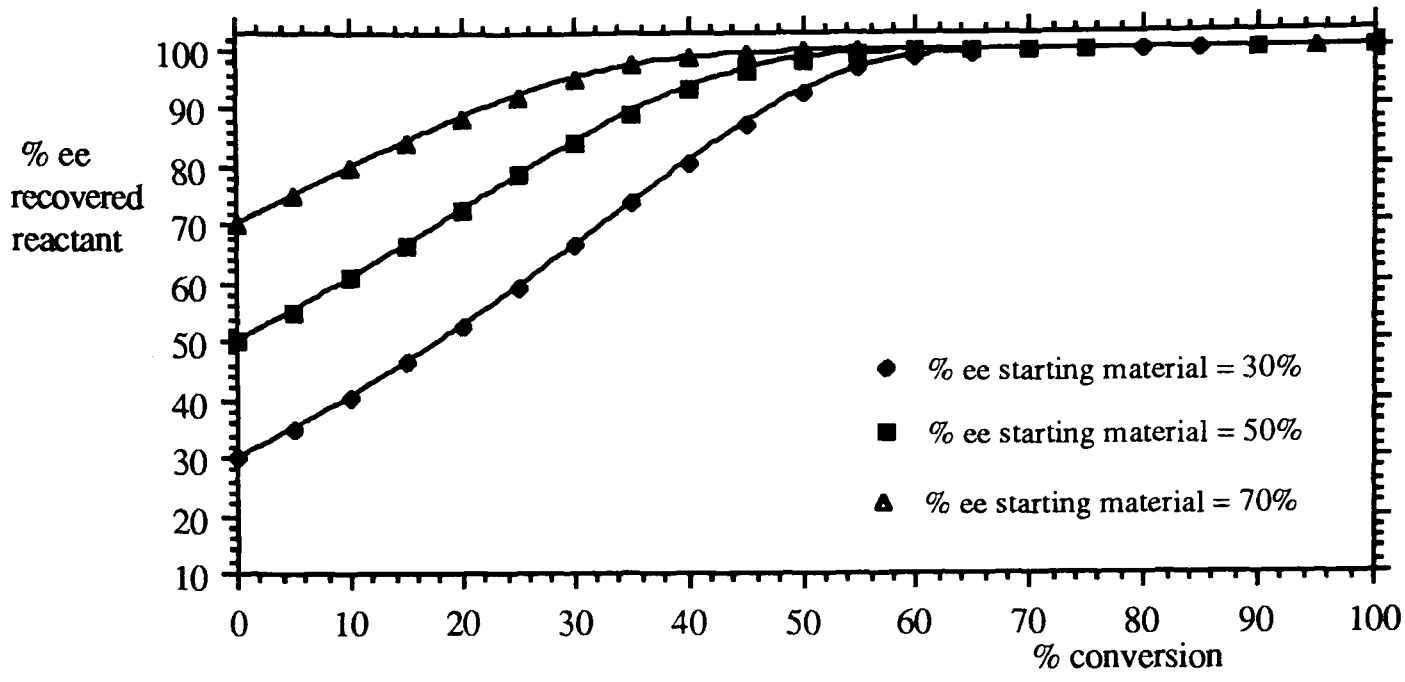
$k_1 = 1$, $k_2 = 3.7$, $k_3 = 12.5$, $k_4 = 205$.

90% ee

1.4.4.3 Use of the Product from the First Kinetic Resolution as Starting Material in a Second Kinetic Resolution in which the Minor Enantiomer is the faster reacting.

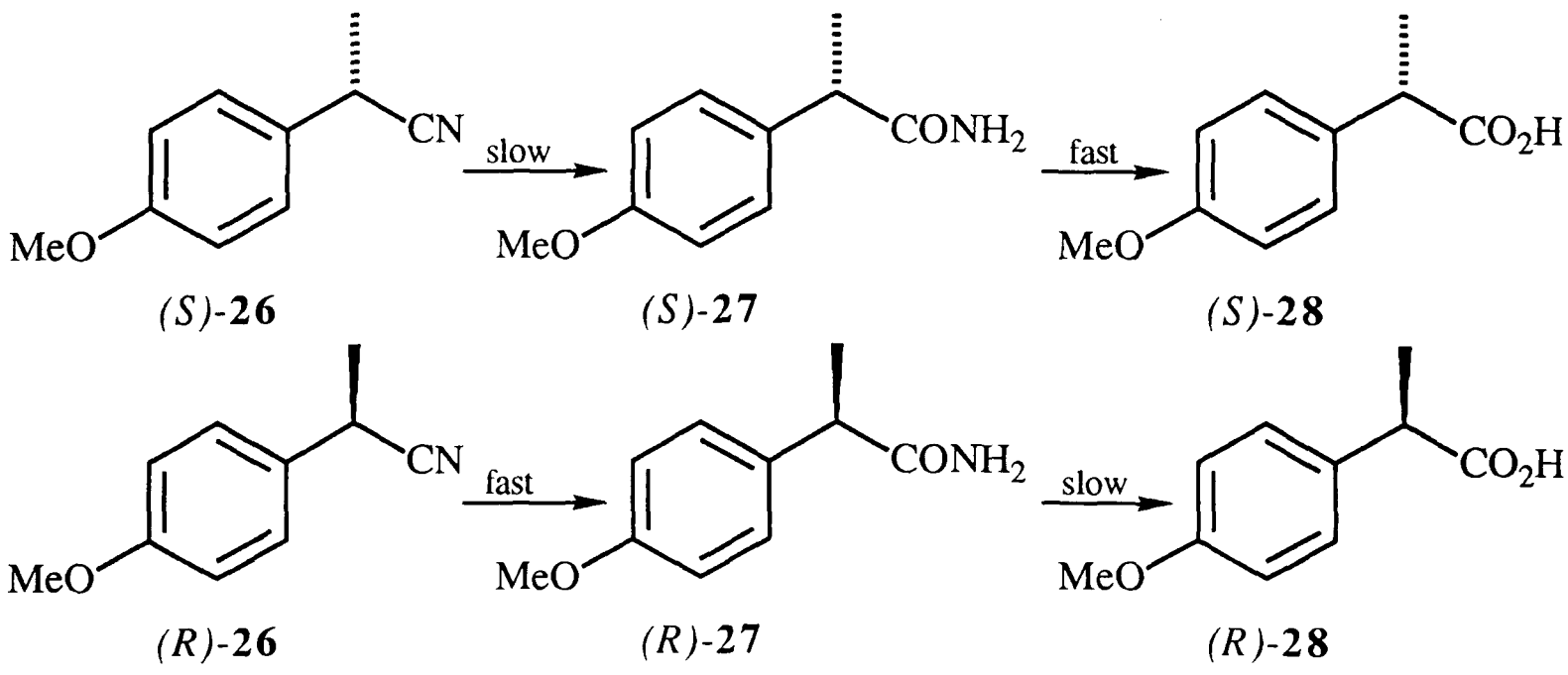
This section also describes a technique in which the product from the first kinetic resolution is used directly as the starting material in the second kinetic resolution. However in these examples, in the second kinetic resolution, the minor enantiomer (present in the starting material) is the faster reacting. This means that the recovered reactant (rather than the product) from the second kinetic resolution can be obtained with higher enantiomeric excesses as shown in **Figure 7**. This approach also has the advantage [over recycling (see Section 1.4.4.1)] that there is one less step involved, although again, it does require that a suitable second kinetic resolution system be available.

Figure 7 : % Enantiomeric excess of reactant vs % conversion for kinetic resolution (E = 10) of a scalemic starting material (where the minor enantiomer is faster reacting).



Ohta *et al.* observed evidence that such a process was occurring when *(RS)*-2-(4-methoxyphenyl)propionitrile (**26**) was treated with *rhodococcus butanica.* In the first step *(R)*-**26** was preferentially converted to the amide (**27**), and in the second step it was found that *(S)*-**27** (the minor enantiomer) was preferentially converted through to the carboxylic acid (**28**). Thus *(R)*-**27** was obtained in 45% yield and with an enantiomeric excess of 99% (**Scheme 14**).[25]

Scheme 14 : Enzymic kinetic resolution of *(RS)*-**26** using *rhodococcus butanica.*



The only other example of this type of process is the pig liver esterase mediated hydrolysis of (±)-*trans*-1,2-diacetoxycyclopentane as reported by Schneider *et al.*[23b]

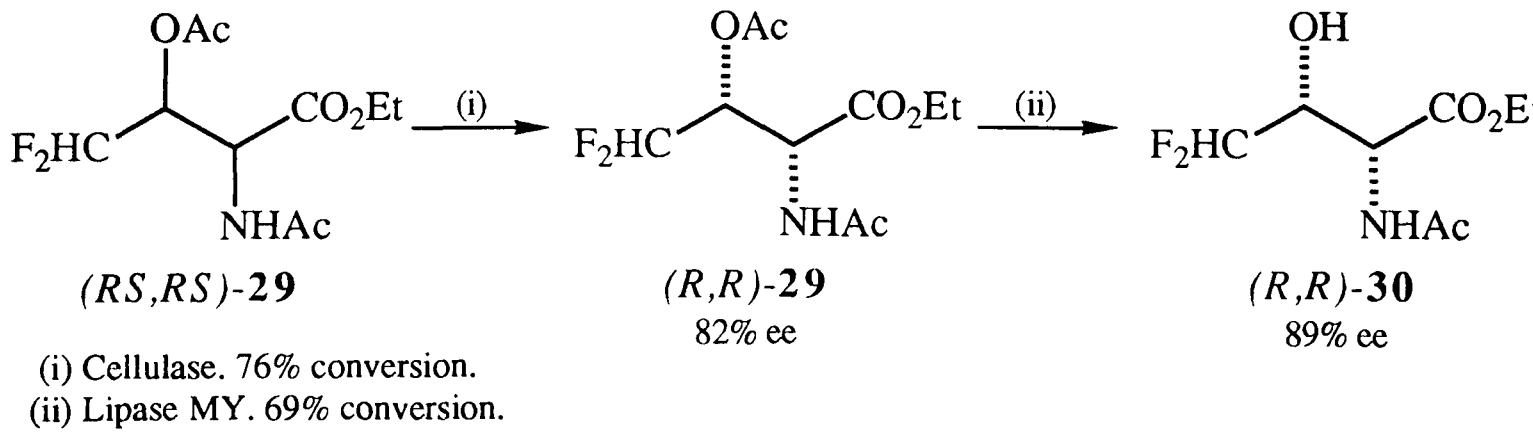
1.4.4.4 Use of the Recovered Reactant from the First Kinetic Resolution as Starting Material in a Second Kinetic Resolution in which the Major Enantiomer is the faster reacting.

If the recovered reactant from a kinetic resolution is used as the starting material in a second kinetic resolution, in which the major enantiomer (present in the starting material) is the faster reacting enantiomer, higher product yields and enantiomeric excesses (when compared with conventional kinetic resolutions) are achievable (see Chapter 2).[26] Isolated examples of this technique have appeared in the chemical literature, however the generality of the concept and the potential benefits to yield and enantiomeric excess have not been fully realised.[8,27]

Variation of % enantiomeric excess of the product from the second kinetic resolution with % conversion is identical to that shown in **Figure 6**.

One example is that performed by Kitazume *et al.* for the preparation of diprotected *(R,R)*-4,4-difluorothreonine (**30**).[28] In the first kinetic resolution *(RS,RS)*-**29** was hydrolysed using cellulase (from *trichoderma viride*). The *S,S* enantiomer of **29** preferentially reacted and after 76% conversion, *(R,R)*-**29** was obtained as the recovered reactant with an enantiomeric excess of 82%. In the second kinetic resolution the scalemic *(R,R)*-**29** (82% ee) was enzymically hydrolysed using lipase MY (which was found to prefentially hydrolyse the *R,R* enantiomer of **29**) to give *(R,R)*-**30**, after 69% conversion, with an enantiomeric excess of 89% (**Scheme 15**).

Scheme 15 : Use of a double kinetic resolution technique for the preparation of diprotected *(R,R)*-4,4-difluorothreonine (**30**).



(RS,RS)-**29**

(R,R)-**29**
82% ee

(R,R)-**30**
89% ee

(i) Cellulase. 76% conversion.
(ii) Lipase MY. 69% conversion.

1.4.5 Combination of Asymmetric Synthesis with Kinetic Resolution.

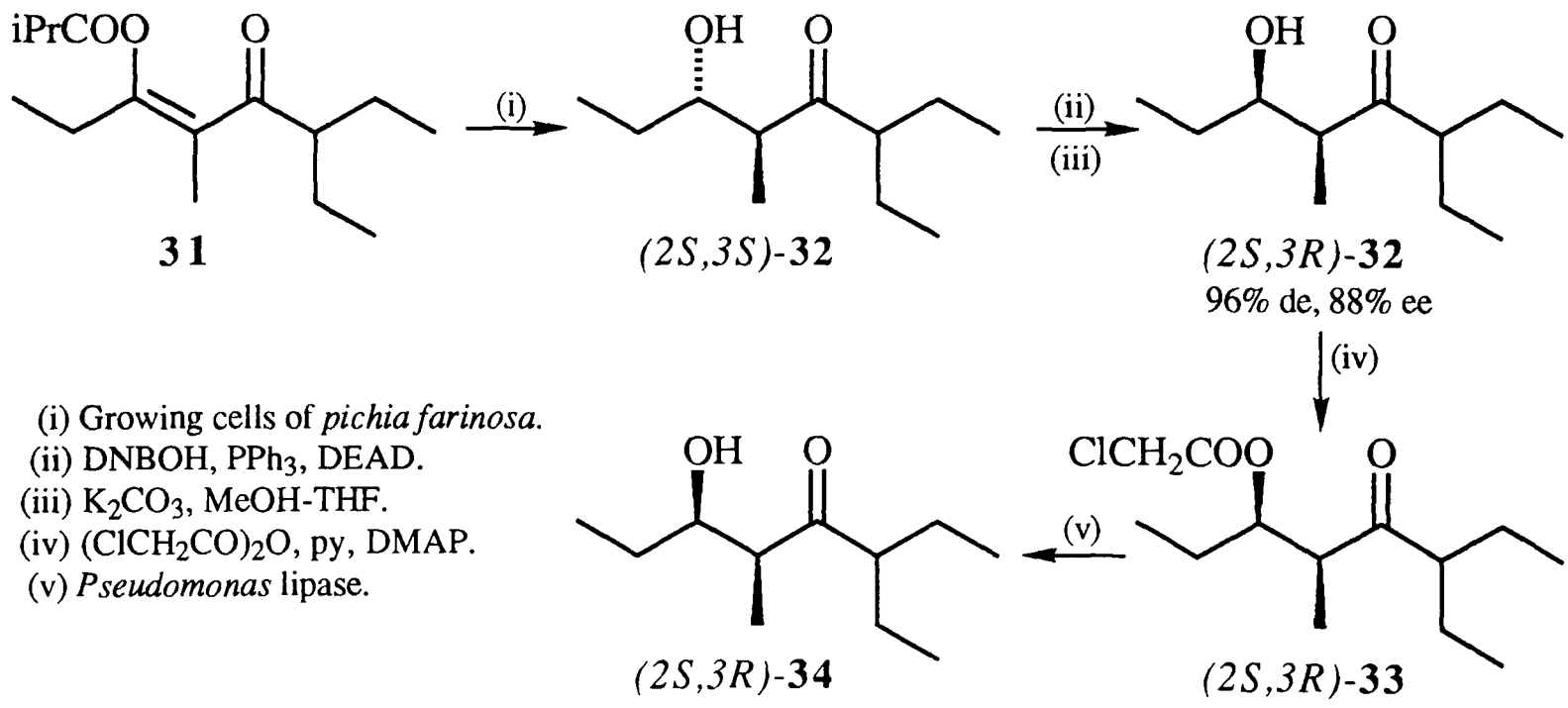
If the scalemic product from an asymmetric synthesis is subjected to a kinetic resolution, it has been shown that material with higher enantiomeric excesses can be obtained. The obvious advantage of this type of process over sequential kinetic resolutions is that the theoretical yield from the first step is 100%. There are two distinct categories into which the processes can be placed.

1.4.5.1 Use of the Product from an Asymmetric Synthesis as Starting Material in a Kinetic Resolution in which the Major Enantiomer is the faster reacting.

In this case (as in Section 1.4.4.2), the product from the kinetic resolution can be obtained with higher enantiomeric excesses.

Apart from the two examples of this type of process described in Chapters 4 and 5, the only other known example is that recently published by Ohta *et al.* in the preparation of *(2S,3R)*-sitopholate (**34**) as shown in **Scheme 16**.[29]

Scheme 16 : Preparation of *(2S,3R)*-sitophilate (**34**) *via* combination of asymmetric synthesis and kinetic resolution.



The asymmetric synthesis step involved reduction of the enol ester (**31**) using the growing cells of *pichia farinosa*. The resulting *(2S,3S)*-β-hydroxy ester (**32**) was then converted, *via* the corresponding 3,5-dinitrobenzoate, to give the *2S,3R* isomer of **32** with

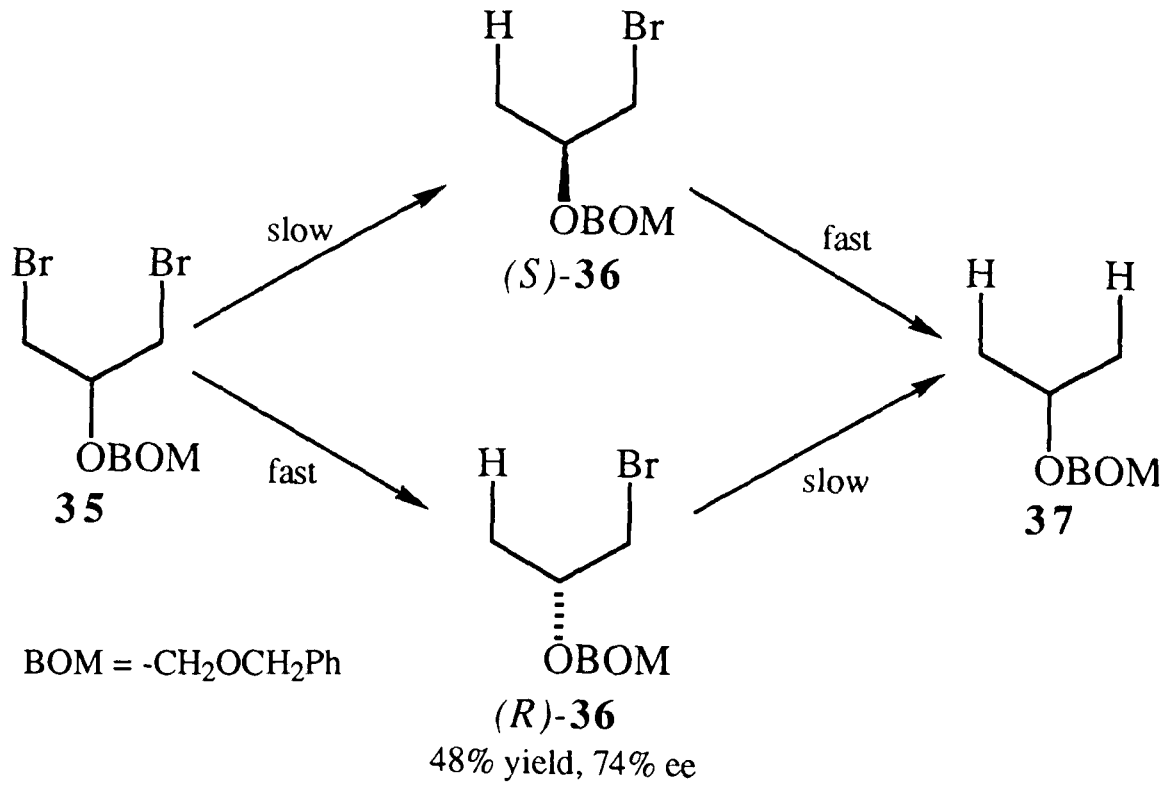
an enantiomeric excess of 88%. Kinetic resolution *via pseudomonas* lipase mediated hydrolysis of the corresponding chloroacetate (**33**) gave *(2S,3R)*-sitophilate (**34**) as the product with an overall yield of 22%; a diastereomeric excess of 98% and an enantiomeric excess of 99%.

1.4.5.2 Use of the Product from an Asymmetric Synthesis as Starting Material in a Kinetic Resolution in which the Minor Enantiomer is the faster reacting.

Here (as in Section 1.4.4.3), the recovered reactant from the kinetic resolution can be obtained with higher enantiomeric excesses.

There are a number of examples in the chemical literature of this type of process. In most cases, the asymmetric synthesis and kinetic resolution proceed in the same reaction medium.[30] The first example was performed by Sih *et al.* and involved enzymic hydrolysis of the meso diester: 1,5-diacetoxy-*cis*-2,4-dimethyl pentane.[31] Other examples include Jäger's and Schreiber's work on the Sharpless epoxidation of divinylcarbinol.[32] More recently, Chong *et al.* observed this type of process when they performed the reduction of a number of prochiral glycerol derivatives such as **35**. Use of a proline derived reducing agent led to formation of the intermediate *(R)*-monobromide (**36**) in 48% yield and with an enantiomeric excess of 74% (**Scheme 17**).[33]

Scheme 17 : Combination of asymmetric synthesis and kinetic resolution.



There are a small number of examples where the two processes are not performed in the same reaction medium. These include the preparation of the pheromone sulcatol as described in Chapter 5; work by Burgess *et al.* where asymmetric synthesis using the SPAC reaction was combined with enzymic kinetic resolution;[34] and also Wong's example for the preparation of monoprotected 2-substituted propan-1,3-diol derivatives (this example is discussed in more in detail in Chapter 4).[35]

1.5 Summary and Objectives.

From the work described it was apparent that certain aspects of kinetic resolution had not been studied in any detail. In particular kinetic resolution of partially resolved materials had received little attention. The initial aim of this project was to investigate these types of kinetic resolution, principally for the preparation of products with enhanced enantiomeric excesses and/or yields.

The mathematical relationships described in **Figure 2** can only be applied to kinetic resolutions where the starting material is racemic. In order to predict the outcome of kinetic resolutions using scalemic starting materials a simple computer model was used (see Appendix 1).[36] Use of this computer model enabled a comparison to be made of the final product enantiomeric excesses and overall yields obtainable by a number of the kinetic resolution strategies described (see Appendix 2).

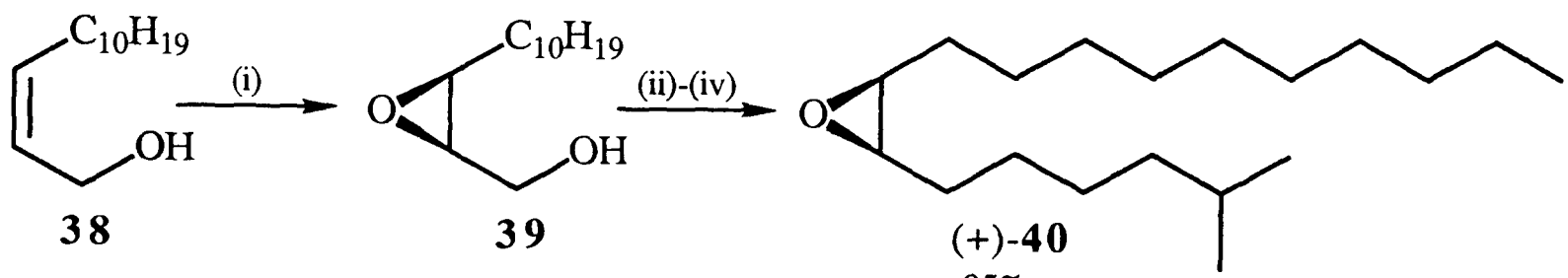
Chapter 2

Enhanced Product Enantiomeric Excesses and Yields in Sharpless Epoxidations by the use of a Double Kinetic Resolution Strategy.

2.1 The Sharpless Epoxidation.

In 1980 Sharpless *et al.* reported one of the most important contributions to modern chemistry, this was of course the asymmetric epoxidation of allylic alcohols.[37] Since the initial work, the Sharpless epoxidation has been widely used in organic synthesis.[38] One of the most striking examples is the preparation of the gypsy moth sex attractant (+)-disparlure (**40**) from the allylic alcohol (**38**) as shown in **Scheme 18**.[39] It has been estimated that the financial saving made during the first two years that (+)-disparlure (**40**) was used by the US government for insect control, exceeded that expended during the ten years that Sharpless spent working on the methodology.[40]

Scheme 18 : Use of the Sharpless epoxidation in the preparation of (+)-disparlure (**40**).



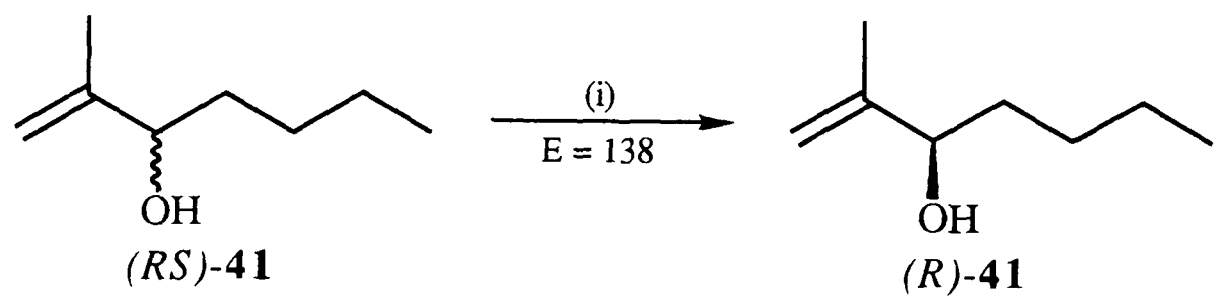
38 **39** (+)-**40**

(i) (-)-DET, TBHP, $Ti(OiPr)_4$, CH_2Cl_2.
(ii) Oxidation.
(iii) Wittig olefination.
(iv) Hydrogenation.

>95% ee
27% Overall yield

Shortly after the first publication, Sharpless reported that kinetic resolution of a number of racemic allylic alcohols proceeded with stereoselectivity factors as high as 138 as shown in **Scheme 19**.[7b]

Scheme 19 : Kinetic resolution of 2-methylhepten-3-ol (**41**) *via* Sharpless epoxidation.

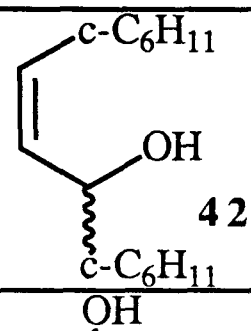
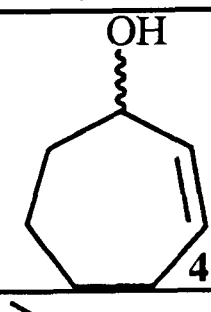
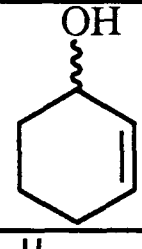
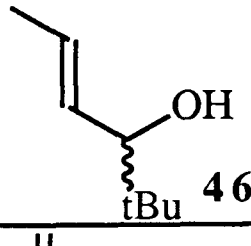
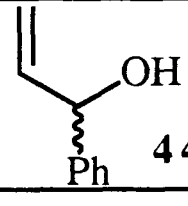
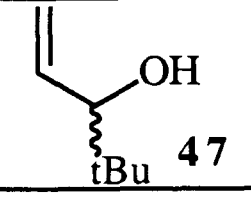


(RS)-**41** *(R)*-**41**

(i) (+)-DiPT, TBHP, $Ti(OiPr)_4$, CH_2Cl_2.

It has, however, been found that some racemic allylic alcohols undergo kinetic resolution much less efficiently as shown in **Table 1**.

Table 1 : Examples of poor substrates for Sharpless kinetic resolution.

Entry	Substrate	E	Entry	Substrate	E
1	 **42**	~1.2[7b,38b]	4	 **45**	16[7b,38b]
2	 **43**	~1.9[7b,38b]	5	 **46**	1.1[41]
3	 **44**	4 - 10[38b]	6	 **47**	1.2[41]

As mentioned previously (see Section 1.3), kinetic resolutions that proceed with low stereoselectivity factors are incapable of yielding products with high enantiomeric excesses. Therefore, for the allylic alcohols (**42** - **47**) shown in **Table 1**, conventional kinetic resolution is of no use if high product enantiomeric excesses are required.

2.2 Proposed Double Kinetic Resolution Strategy.

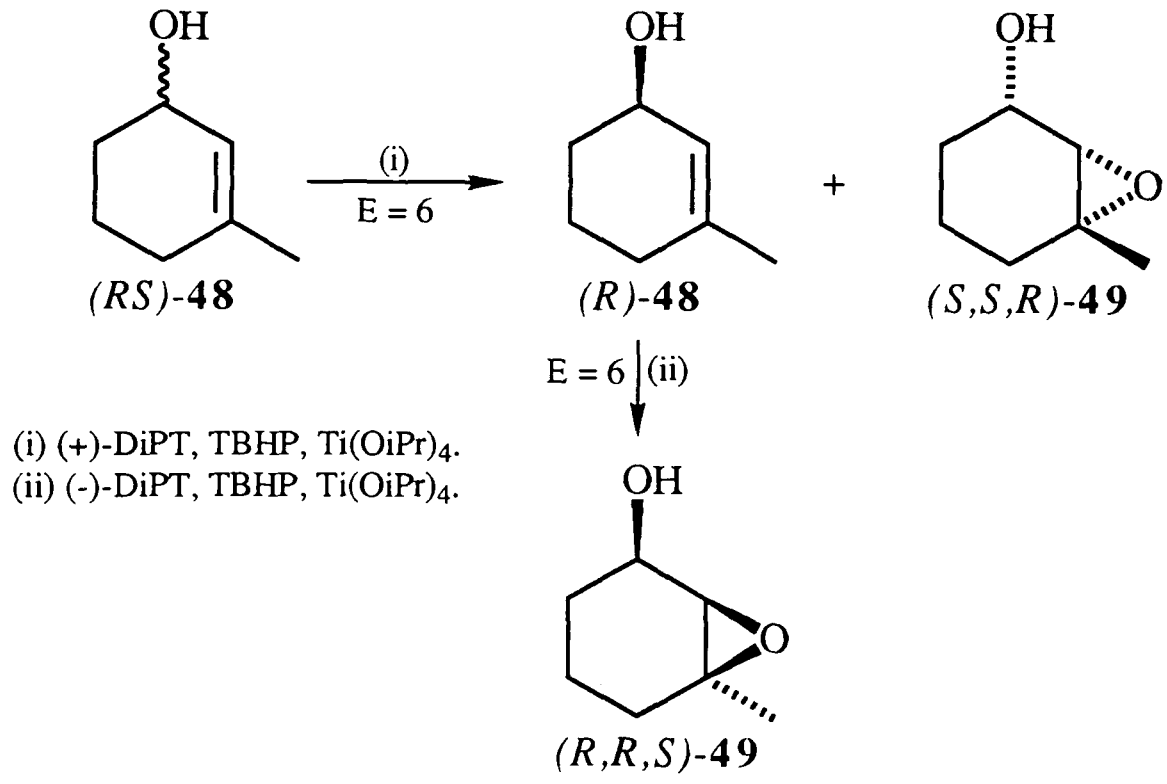
The Sharpless epoxidation uses tartaric acid derivatives as its source of chirality. Since both enantiomers of tartaric acid are readily available, it was thought that a double kinetic resolution strategy could be applied. It was anticipated that this would enable formation of products with higher enantiomeric excesses and/or yields than those obtainable by conventional kinetic resolution methods. The particular double kinetic resolution strategy proposed was one in which the recovered reactant from the first kinetic resolution was used as the starting material for the second kinetic resolution (see Section 1.4.4.4). In the second kinetic resolution the source of chirality would be the opposite

enantiomer of the tartaric acid derivative used in the first kinetic resolution (**Scheme 20**). Therefore, in the second kinetic resolution the enantiomer in which the starting material was enriched would be the faster reacting enantiomer.

In addition to the allylic alcohols shown in **Table 1**, it was known that 3-methylcyclohex-2-en-1-ol (**48**) undergoes Sharpless epoxidation with a stereoselectivity factor of 6. It was thought that this would be a suitable substrate on which to demonstrate the proposed double kinetic resolution strategy.[42]

The enantiomeric excess of the recovered reactant increases as the kinetic resolution proceeds. Therefore higher product enantiomeric excesses could be obtained by simple non-selective epoxidation (E = 1) of the recovered reactant, for example with vanadyl acetoacetate and *t*-butylhydroperoxide.[43] Calculations performed using the computer model (see Appendix 1) indicated that increased yields and/or enantiomeric excesses are achievable if the double kinetic resolution strategy described is used (**Scheme 20**).

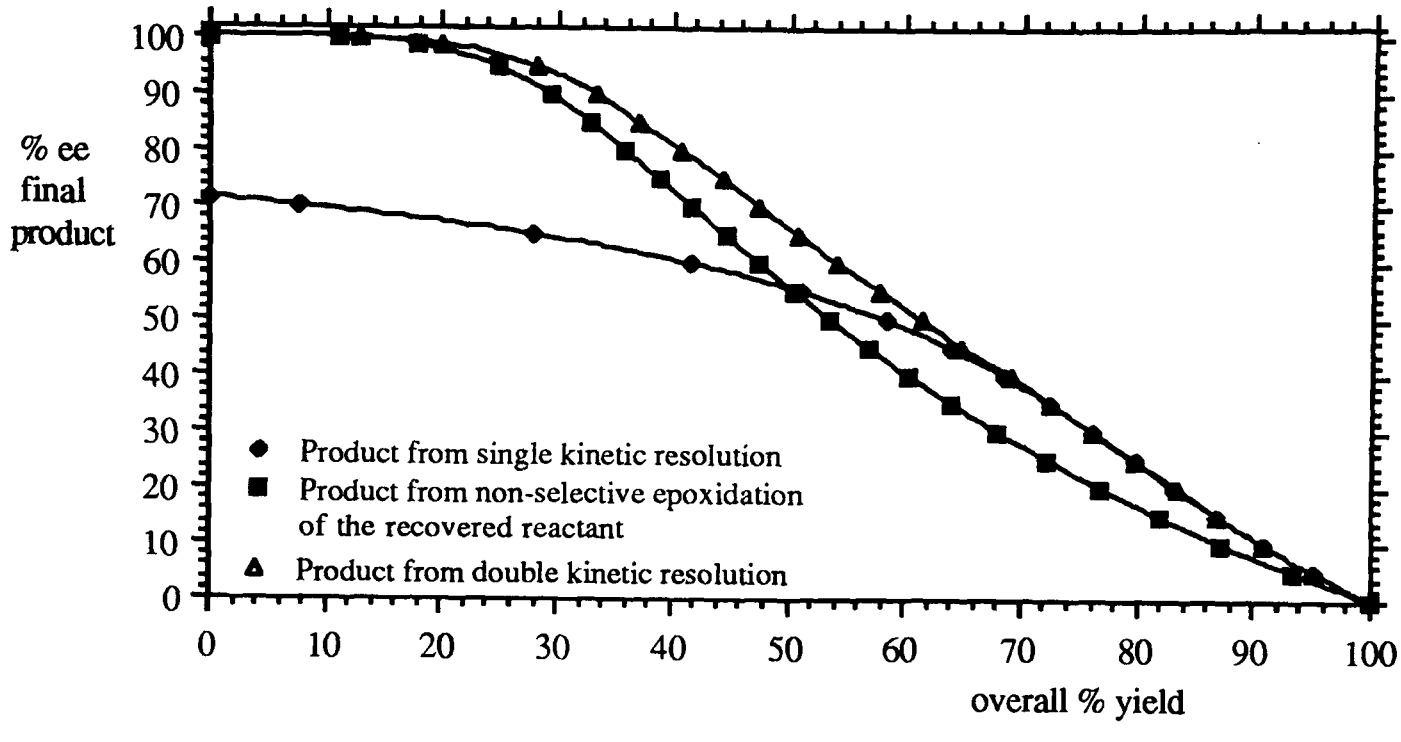
Scheme 20 : Proposed double kinetic resolution using the Sharpless epoxidation.



The overall maximum theoretical yields obtainable for any product enantiomeric excess by this double kinetic resolution strategy (when E = 6 for each step) are compared graphically with the theoretical product yields available by conventional methods (when E =

6) in **Figure 8** (for details of how **Figure 8** was obtained see Appendix 3). The enantiomeric excess of the final product from a double kinetic resolution depends on the stereoselectivity factor and the extent of reaction for each step.

Figure 8 : Comparison of theoretical product yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy.



As can be seen from **Figure 8**, maximum product enantiomeric excess from a single step kinetic resolution (when E = 6) is 71% (obtainable at an infinitesimally small conversion and therefore with an infinitesimally small yield). Use of non-selective epoxidation of the recovered reactant enables products with high enantiomeric excesses to be obtained. However, the double kinetic resolution strategy can lead to product formation with enhanced enantiomeric excesses and/or yields. For example, if product (**49**) with an enantiomeric excess of 85% is required, the theoretical yield obtainable by non-selective epoxidation of the recovered reactant is 33%. Whereas for the same enantiomeric excess, use of the double kinetic resolution strategy gives a theoretical yield of 37%. Alternatively for the same yield of 33%, double kinetic resolution can be performed to give a product with an enantiomeric excess of 90%.

Table 2 compares the overall theoretical yields possible using this double kinetic resolution strategy for various enantiomeric excesses with the yields possible by conventional methods.

Table 2 : Comparison of overall theoretical yields obtainable using this double kinetic resolution strategy (E = 6 for each step) with those obtainable by conventional methods.

% ee of final product.	% Overall yield by conventional methods.[a]	% Overall yield by double kinetic resolution.
70	42	48
75	39	44
80	36	41
85	33	37
90	29	33
95	25	28
99	18	20
99.9	11	13

[a] Non-selective epoxidation of the recovered reactant.

As can be seen from **Table 2**, even for high final product enantiomeric excesses this double kinetic resolution strategy shows significant improvement in yield over conventional methods.

It should be noted that the only difference between non-selective epoxidation of the recovered reactant and the double kinetic resolution strategy is the catalyst used in the second step, in particular the same number of isolation and separation steps are involved. The theoretical benefits should therefore be realisable in practice.

2.3 Application of the Proposed Double Kinetic Resolution Strategy.[44]

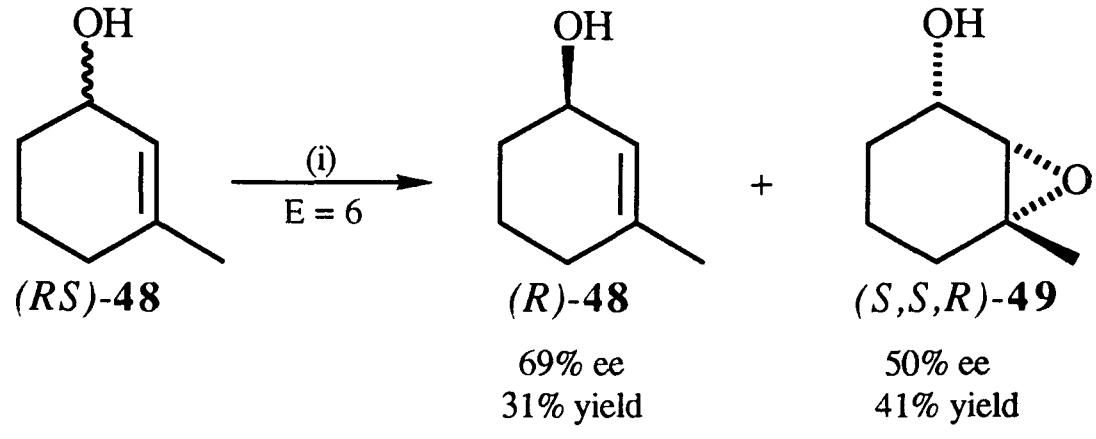
Calculations as shown in **Table 3** using the computer model (Appendix 1) indicated that, for a final product enantiomeric excess of 85% (when E = 6 for both kinetic resolutions), maximum yield using the double kinetic resolution strategy described above would be obtained by allowing the first kinetic resolution to run to 56 - 58% conversion and the second kinetic resolution to run to 84 - 88% conversion.

Table 3 : Calculation of the % conversion required (in each kinetic resolution) to give the maximum possible overall yield of product with 85% ee by double kinetic resolution.

% Conversion in first kinetic resolution.	% ee of recovered reactant from first kinetic resolution.	% Conversion in second kinetic resolution to give a product with 85% ee.	% Overall yield.
50	55.5	65	32.5
55	63.9	81	36.5
56	65.7	84	37.0
57	67.4	86	37.0
58	69.1	88	37.0
59	70.9	90	36.9
60	72.7	92	36.8
61	74.4	94	36.7
62	76.1	95	36.1

With this in mind, double Sharpless kinetic resolution of *(RS)*-3-methylcyclohex-2-en-1-ol (**48**) was performed. In the first kinetic resolution (+)-diisopropyl tartrate (DiPT) was used as the source of chirality (**Scheme 21**) and after the epoxidation had proceeded to the required (58%) conversion (conversion was monitored by GLC using nonane as an internal standard), the reaction was stopped. Non-acidic workup[45] and flash chromatography enabled isolation of the recovered reactant [*(R)*-**48**] in 31% yield and the epoxide product [*(S,S,R)*-**49**] in 41% yield. Enantiomeric excesses of the recovered reactant (**48**) and product (**49**) were measured by ^{19}F NMR spectroscopy of Mosher's ester derivatives[46] and by comparison of specific rotations with the literature value.[47] The recovered reactant (**48**) had an enantiomeric excess of 69% and the product (**49**) had an enantiomeric excess of 50%.

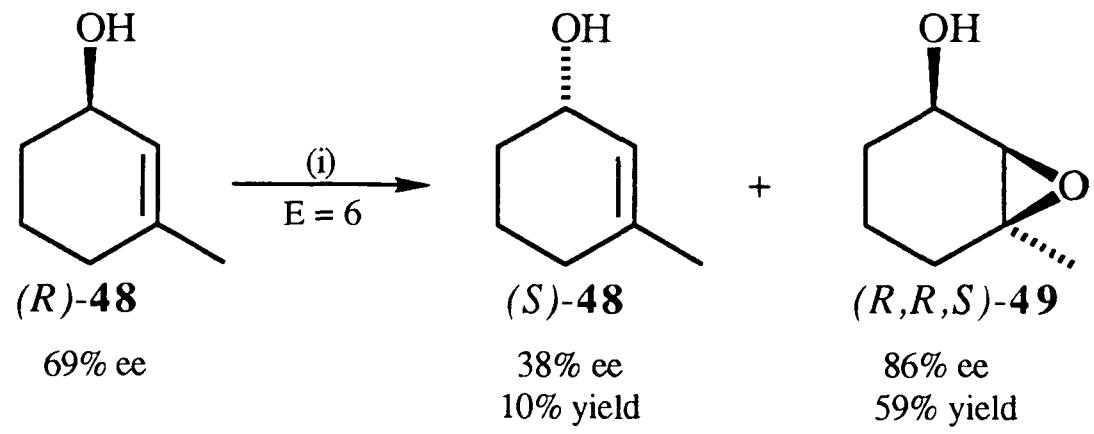
Scheme 21 : First kinetic resolution.



(i) (+)-DiPT, TBHP, $Ti(OiPr)_4$, CH_2Cl_2. 58% conversion.

The recovered reactant [*(R)*-**48**] (69% ee) from the first kinetic resolution was used as the starting material in the second kinetic resolution where (-)-DiPT was used as the source of chirality (**Scheme 22**). Once again, the extent of the reaction was monitored by GLC and at the appropriate conversion (86%) the reaction was halted. Non-acidic workup followed by flash chromatography gave recovered starting material [*(S)*-**48**] in 10% yield with an enantiomeric excess of 38% (model predicted 35%) and the required product [*(R,R,S)*-**49**] in 59% yield with an enantiomeric excess of 86%.

Scheme 22 : Second kinetic resolution.



(i) (-)-DiPT, TBHP, $Ti(OiPr)_4$, CH_2Cl_2. 86% conversion.

If the opposite product enantiomer was required it could be obtained by simply reversing the order in which the enantiomers of diisopropyl tartrate were used.

2.4 Consideration of this Double Kinetic Resolution Strategy for a Range of Stereoselectivity Factors.

Using data obtained from the computer model (Appendix 1), a series of plots was made for a range of stereoselectivity factors comparing the overall theoretical yields and product enantiomeric excesses obtainable by this double kinetic resolution strategy, with those obtainable by conventional kinetic resolution methods (**Figures 9** to **12**, see also **Figure 8**). **Figures 9** to **12** were prepared using the same method as used for **Figure 8** (see Appendix 3).

It is apparent from **Figures 9** to **12** that as the stereoselectivity factor increases, the benefits of this double kinetic resolution strategy diminish.

Figure 9 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy.

(E = 3 for each step).

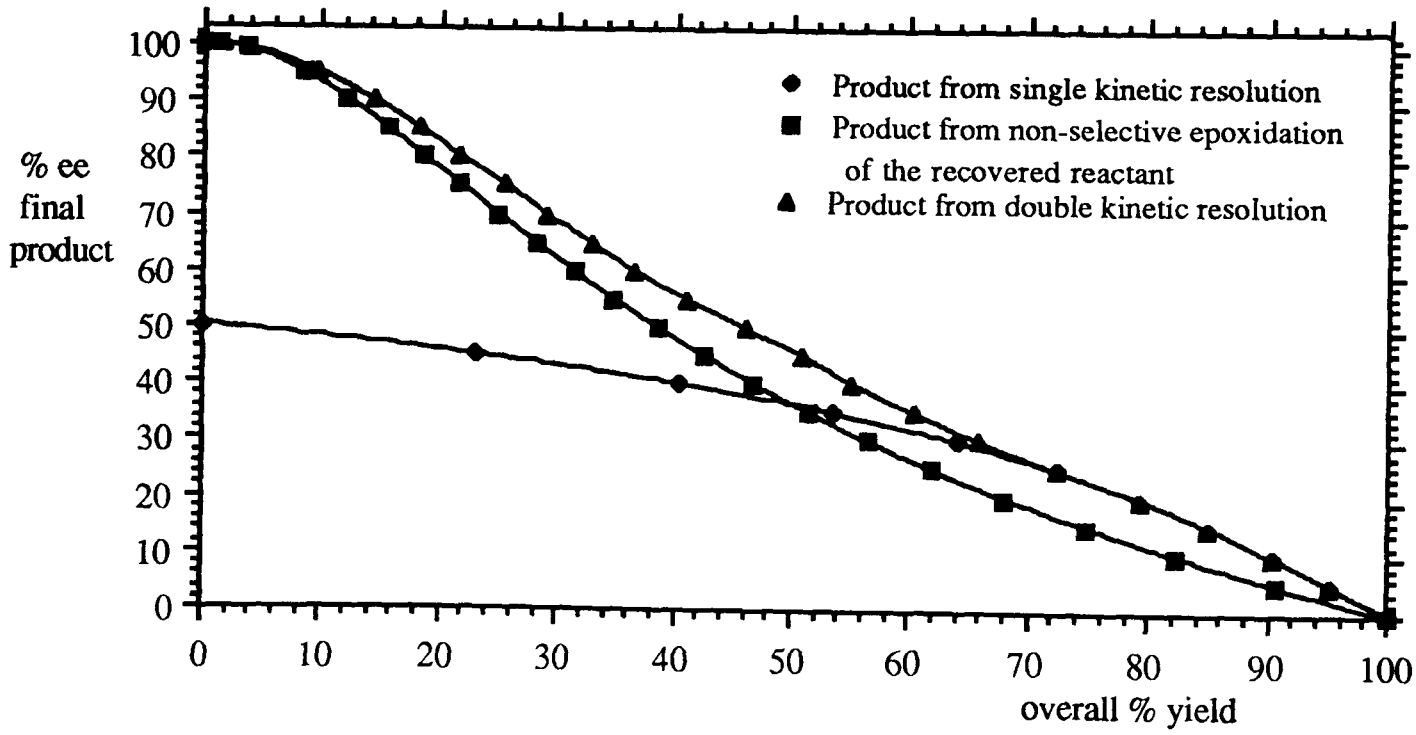


Figure 10 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 10 for each step).

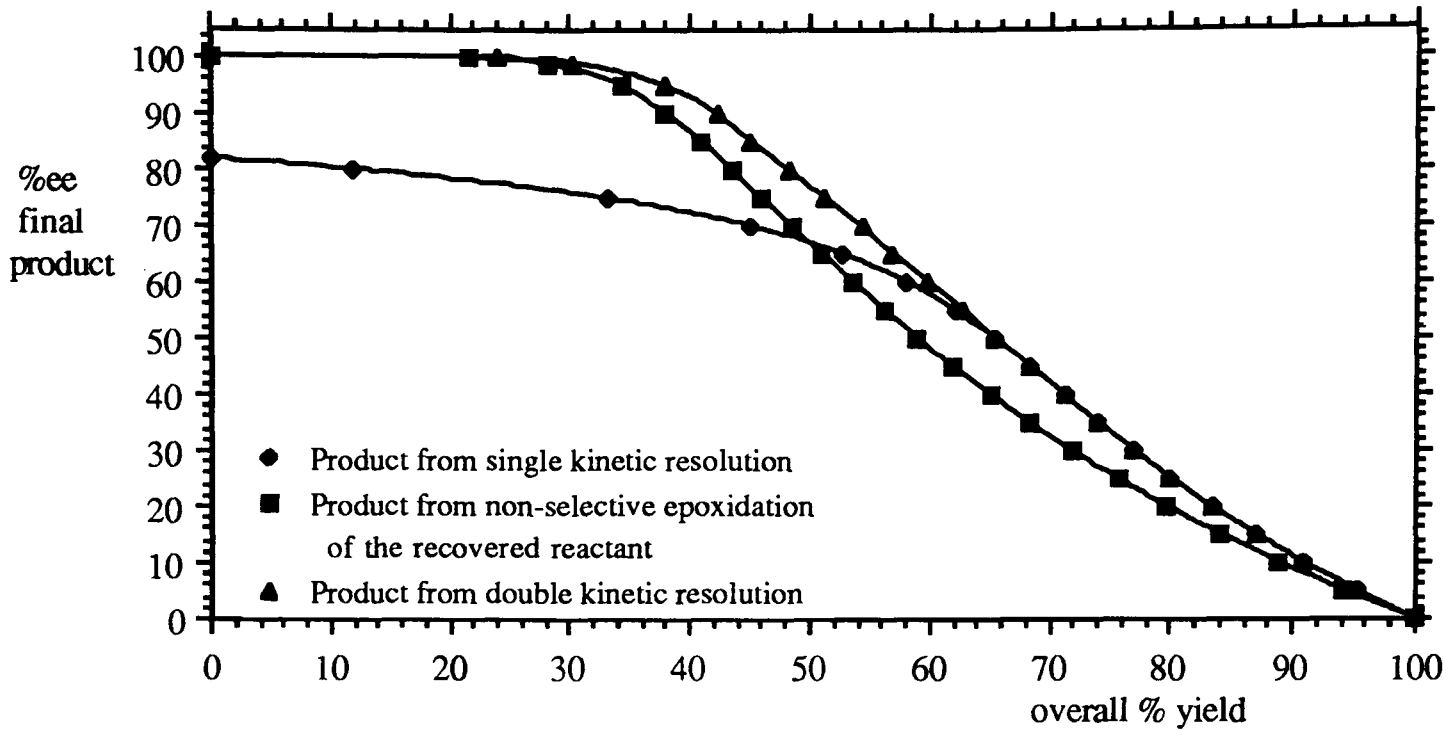


Figure 11 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 15 for each step).

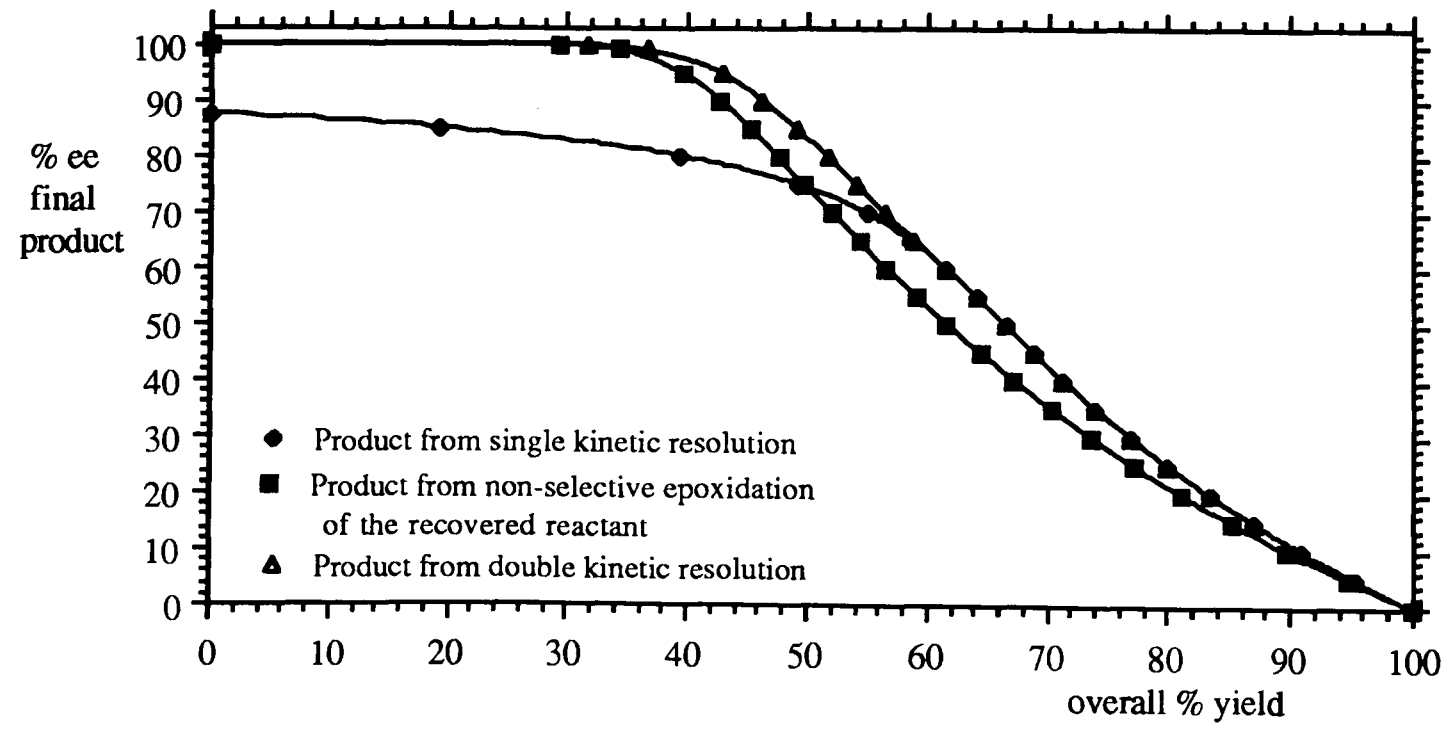
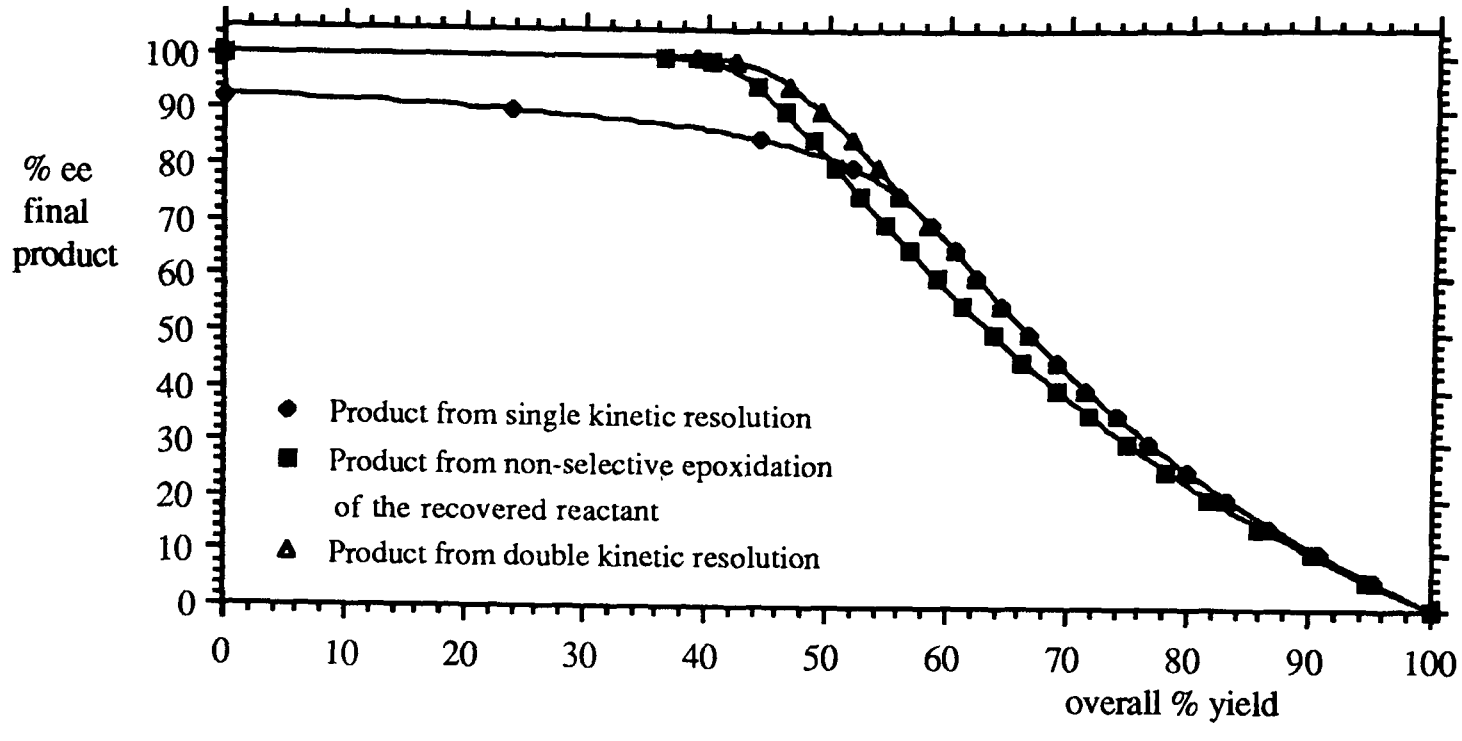


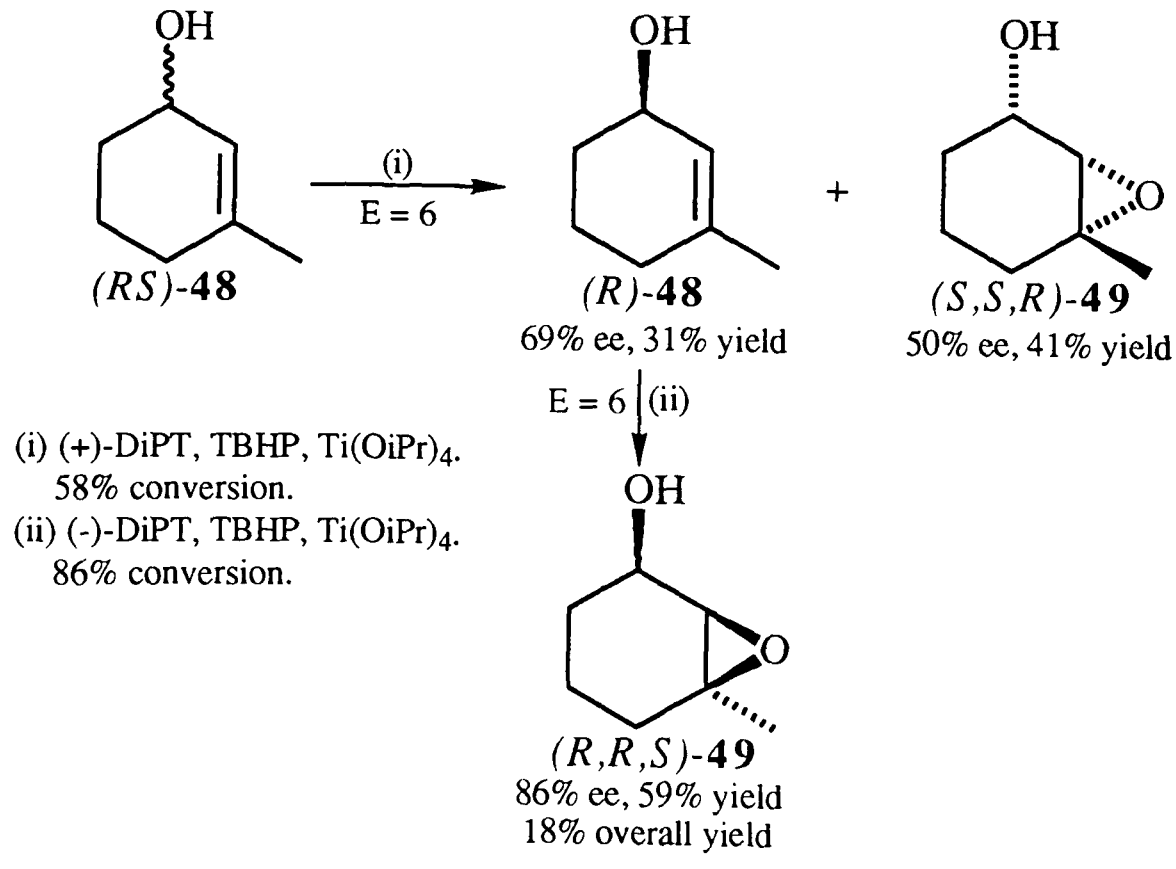
Figure 12 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 25 for each step).



2.5 Summary and Conclusion.

Application of a double kinetic resolution strategy where the recovered reactant from the first kinetic resolution was used as the starting material in a second kinetic resolution, in which the opposite enantiomer of the homochiral reagent was deployed, has been shown to enable formation of product with enhanced enantiomeric excess.

Scheme 23 : Summary.



The main criterion required for this double kinetic resolution strategy to be feasible is that both enantiomers of the homochiral catalyst or reagent are available.

For a comparison of this double kinetic resolution strategy with a number of other double kinetic resolution strategies see Appendix 2.

Chapter 3

Enhanced Product Enantiomeric Excesses and Yields in Lipase Mediated Reactions by the use of a Double Kinetic Resolution Strategy.

3.1 Use of Enzymes in Organic Synthesis.

The value of enzymes for the preparation of homochiral materials is becoming increasingly recognised.[48] Enzymes frequently offer many advantages over conventional chemical reagents. They normally operate under mild conditions, often at room temperature and neutral pH. They are highly efficient catalysts. As far as the preparation of homochiral material is concerned, the most important advantage of enzymes is their great selectivity. Despite these advantages, the use of enzymes in organic synthesis prior to the last ten to fifteen years was minimal. According to Suckling[49] this can partially be explained by the opinions of eminent chemists such as Fleming[50] who referred in 1973 to micro-organisms thus:

> *"Actually, this synthesis, using a microbiological oxidation, is not a total synthesis, even in principle; the use of micro-organisms which have not themselves been synthesised disqualifies the route as a total synthesis in the usually accepted academic sense."*

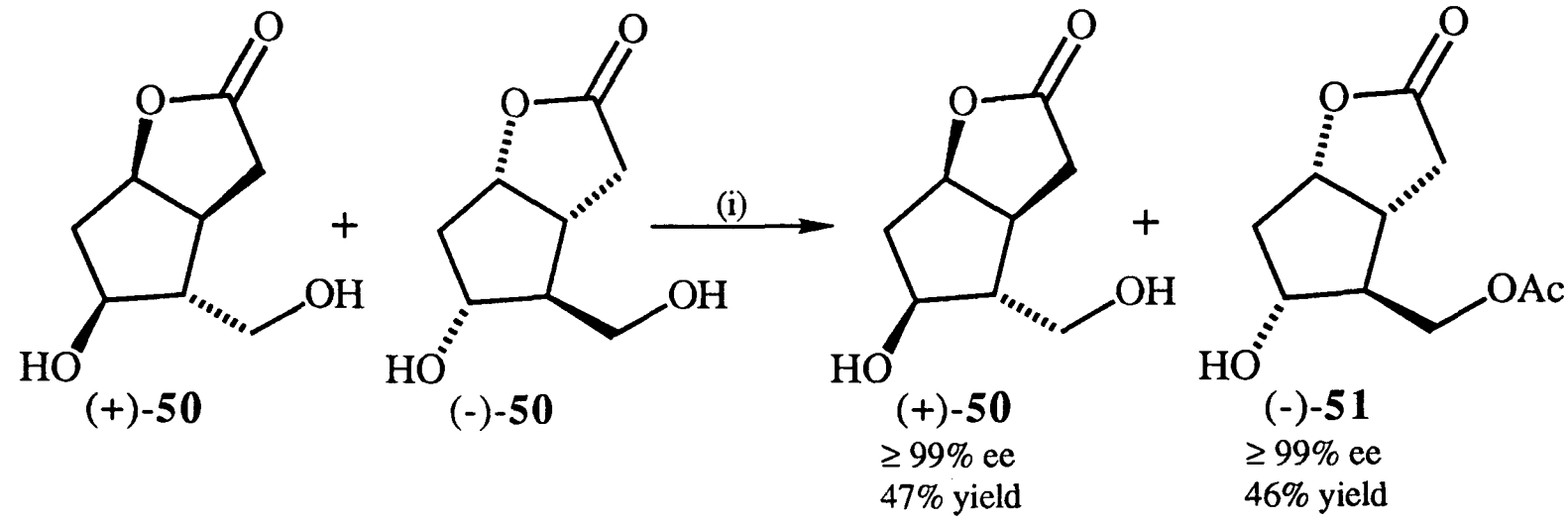
However in recent years, the ready availability of highly selective, stable enzymes and the ever increasing interest in enantioselectivity has led to a huge growth in the use of biocatalytic reactions.

3.1.1 Lipase mediated Hydrolysis and Esterification.

Enzymes have found widespread use as catalysts for the stereoselective hydrolysis of esters and the stereoselective esterification of alcohols.[51] The enzymes that mediate these reactions are known as lipases and esterases.

An example of the great utility of these reactions is the preparation of the Corey lactone derivatives (**50** to **53**) in homochiral form. These key intermediates in the synthesis of prostaglandins were prepared by kinetic resolution using lipase AK and lipase PS. Both lipase mediated esterification and hydrolysis proceeded with very high stereoselectivity factors (E > 1000) and excellent yield as shown in **Scheme 24**.[52]

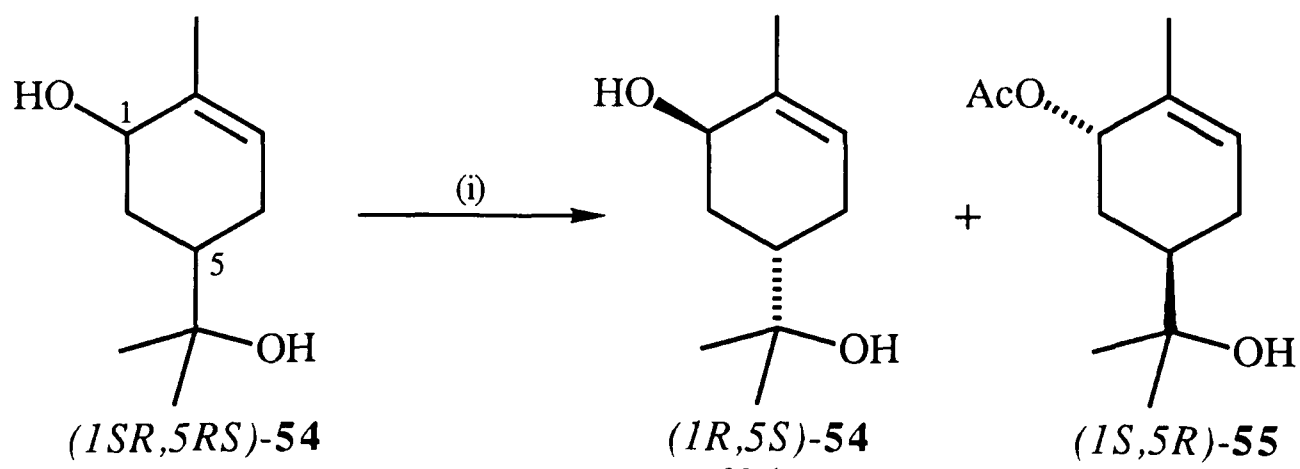
Scheme 24 : Preparation of homochiral Corey lactone derivatives (**50** to **53**) *via* lipase mediated kinetic resolutions.



(i) Lipase AK, vinyl acetate, CH_2Cl_2.
(ii) (R = TBDMS) lipase PS, pH 7.6 buffer.

Carrea *et al.* used lipase mediated esterification to kinetically resolve the mucolytic drug *(1SR,5RS)*-sobrerol (**54**). Once again the reaction proceeded with high stereoselectivity factor (E = 518) and yield as shown in **Scheme 25**.[53]

Scheme 25 : Preparation of homochiral sobrerol (**54**) *via* lipase mediated esterification.

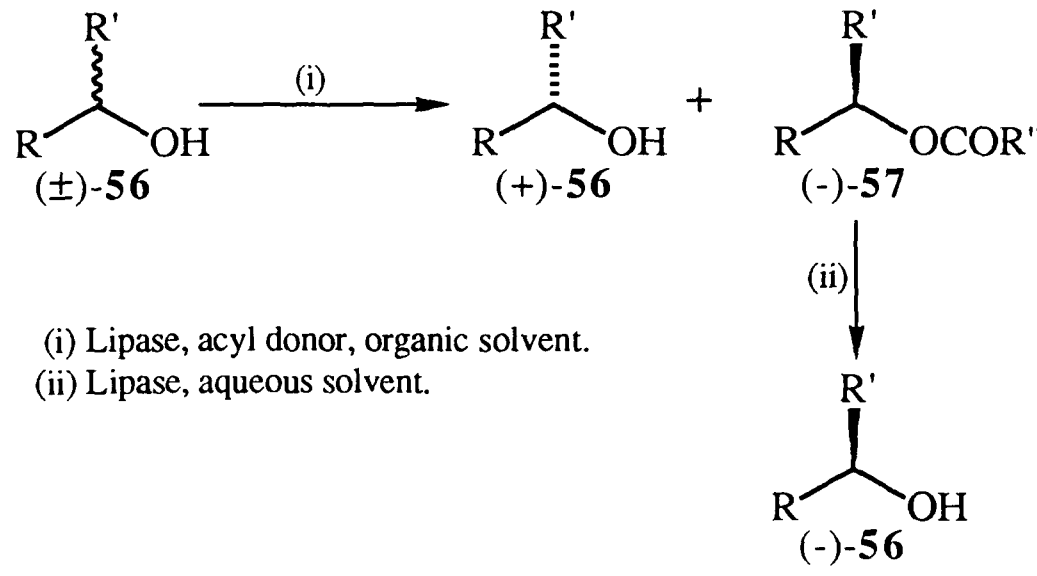


(i) Lipase PS, vinyl acetate, $(CH_3)_3CCH_2OH$.

3.2 Proposed Double Kinetic Resolution Strategy.

As with the Sharpless epoxidation (Chapter 2), there are examples of lipase mediated kinetic resolutions that proceed with low stereoselectivity factors and are therefore incapable of yielding products with high enantiomeric excesses. It was anticipated that use of a double kinetic resolution strategy would enable formation of product with higher enantiomeric excesses and/or yields than those obtainable by conventional kinetic resolution methods. Since both enantiomers of the homochiral catalyst (the lipase) are not available the double kinetic resolution strategy used for Sharpless epoxidations is not possible. In this case, the particular double kinetic resolution strategy proposed was one in which the product from the first kinetic resolution was used as the starting material for the second kinetic resolution. The first kinetic resolution would be a lipase mediated esterification of a racemic alcohol (**56**), and in the second kinetic resolution, the scalemic ester product (**57**) (from the first kinetic resolution) would be used as the starting material in a lipase mediated hydrolysis (**Scheme 26**) (see Section 1.4.4.2). If the same lipase was used in each step it was expected that in the second kinetic resolution, the enantiomer in which the starting material was enriched would be the faster reacting enantiomer.

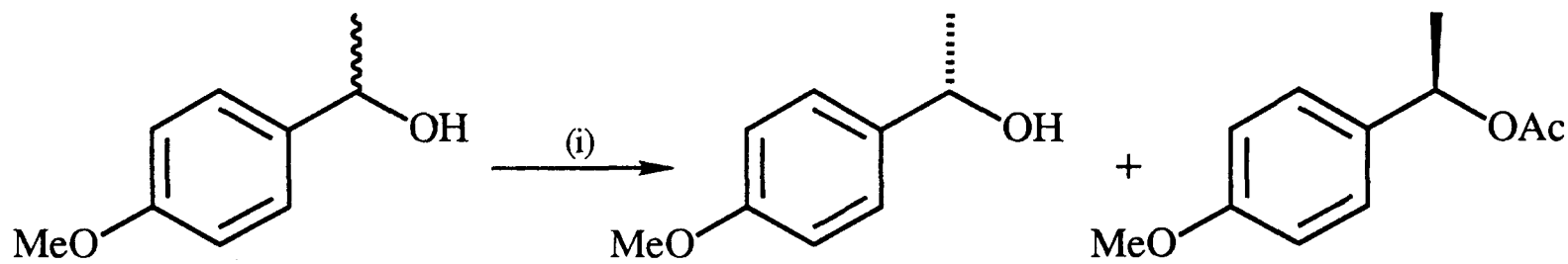
Scheme 26 : Proposed double kinetic resolution using lipase mediated reactions.



Calculations using the computer model (Appendix 1) indicated that use of the proposed double kinetic resolution strategy (**Scheme 26**) would allow increased yields and/or enantiomeric excesses to be obtained.

From the chemical literature it was thought that 1-(4-methoxyphenyl)ethanol (**58**) would be a suitable substrate on which to demonstrate this double kinetic resolution strategy.[54] In order to find the most suitable lipase, kinetic resolutions of *(RS)*-**58** and of the corresponding acetate of **58** [*(RS)*-**59**] were performed with a number of lipases: *pseudomonas fluorescens* lipase (PFL); pig pancreatic lipase (PPL) and *candida cylindracea* lipase (CCL). Esterification of *(RS)*-**58** in dichloromethane using vinyl acetate as acyl donor proceeded as shown in **Scheme 27**. With each of the lipases used, the *R* enantiomer of **58** was found to be the faster reacting enantiomer.

Scheme 27 : Enzymic esterification of 1-(4-methoxyphenyl)ethanol (**58**).



(RS)-**58** *(S)*-**58** *(R)*-**59**

(i) Lipase, vinyl acetate, CH_2Cl_2.

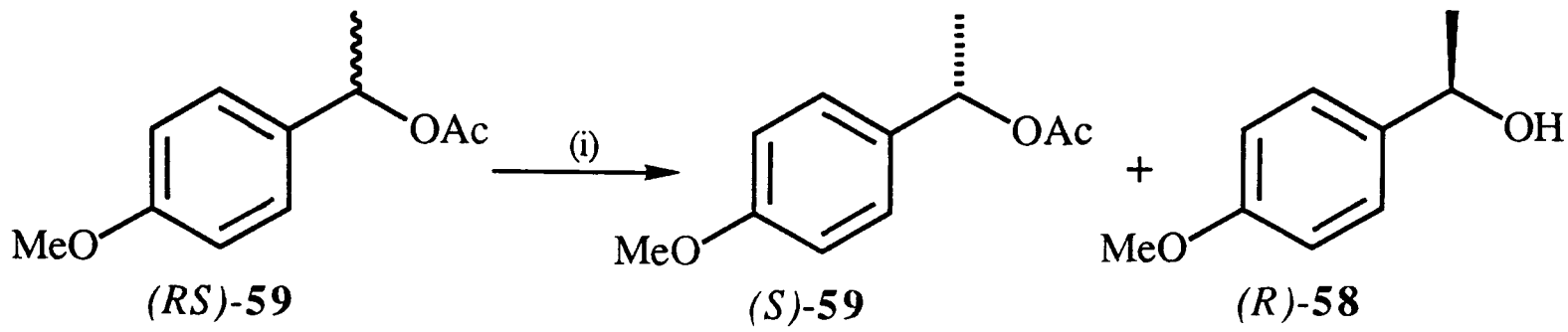
Lipase	% Conversion[a]	% ee Recovered reactant (**58**)[b]	% ee Product (**59**)[c]	E_R[d]	E_P[d]
PFL	44	61	77	14.7	14.1
PPL	30	21	/	3.6	/
CCL	20	10	/	2.6	/

[a] Measured by ^1H NMR spectroscopy of the crude product. [b] Measured by use of the chiral shift reagent:(+)-Eu(hfc)$_3$ followed by ^1H NMR spectroscopy or by preparation of Mosher's ester derivatives[46] followed by ^1H or ^{19}F NMR spectroscopy. [c] Measured as described for **58** after hydrolysis (K_2CO_3/MeOH). [d] Calculated using the standard formulae.[7a]

With PFL, kinetic resolution of *(RS)*-**58** proceeded with a stereoselectivity factor of 15. Esterifications of *(RS)*-**58** with PPL and CCL were found to proceed very slowly and with lower stereoselectivity factors than that found with PFL.

Enzymic hydrolysis (pH 7) of *(RS)*-1-(4-methoxyphenyl)ethyl acetate (**59**) proceeded as shown in **Scheme 28**. As expected, the *R* enantiomer of **59** was found to be the faster reacting enantiomer.

Scheme 28 : Enzymic hydrolysis of 1-(4-methoxyphenyl)ethyl acetate (**59**).



(RS)-**59** *(S)*-**59** *(R)*-**58**

(i) Lipase, pH 7 buffer.

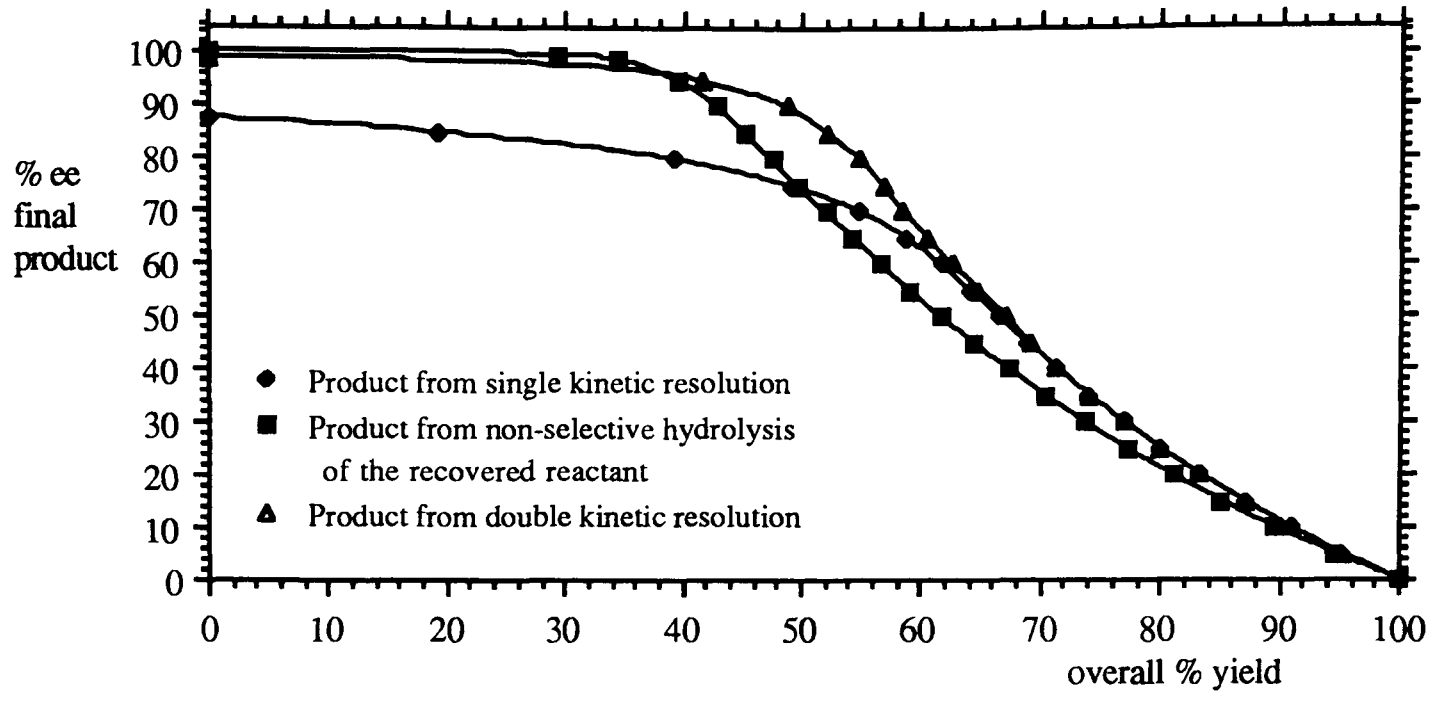
Lipase	% Conversion[a]	% ee Recovered reactant (**59**)[b]	% ee Product (**58**)[c]	E_R[d]	E_P[d]
PFL	51	77	73	15.3	14.4
PPL	61	28	32	1.8	3.1
CCL	40	8	30	1.4	2.2

[a] Measured by ^{1}H NMR spectroscopy of the crude product. [b] Measured as described for **58** after hydrolysis (K_2CO_3/MeOH). [c] Measured by use of the chiral shift reagent: (+)-Eu(hfc)$_3$ followed by ^{1}H NMR spectroscopy or by preparation of Mosher's ester derivatives[46] followed by ^{1}H or ^{19}F NMR spectroscopy. [d] Calculated using the standard formulae.[7a]

As with the esterification of **58**, PFL was found to be the most selective of the three lipases tried. Therefore it was decided that PFL would be used to demonstrate the proposed double kinetic resolution strategy.

The overall maximum theoretical yields obtainable for any product enantiomeric excess by this double kinetic resolution strategy (when E = 15 for each step) are compared graphically with the theoretical product yields available by conventional methods (when E = 15) in **Figure 13** (for details of how **Figure 13** was prepared see Appendix 4). Once again, as with the double kinetic resolution strategy described in Chapter 2, the enantiomeric excess of the final product from this double kinetic resolution depends on the stereoselectivity factor and the extent of reaction for each step.

Figure 13 : Comparison of theoretical product yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy.



As can be seen from **Figure 13**, maximum product enantiomeric excess from a single step kinetic resolution (when E = 15) is 87.5% (obtainable at an infinitesimally small conversion and therefore with an infinitesimally small yield). Use of non-selective hydrolysis of the recovered reactant from the first kinetic resolution would enable products with high enantiomeric excesses to be obtained. However the double kinetic resolution strategy described can lead to product formation with enhanced enantiomeric excesses and/or yields. For example if product (**58**) with an enantiomeric excess of 95% is required, the theoretical yield obtainable by non-selective hydrolysis of the recovered reactant from the first kinetic resolution is 39%. Whereas for the same enantiomeric excess, use of the double kinetic resolution strategy gives a theoretical yield of 42%.

Table 4 compares the overall theoretical yield possible using this double kinetic resolution strategy for various enantiomeric excesses with the yields possible by conventional methods.

Table 4 : Comparison of overall theoretical yields obtainable using this double kinetic resolution strategy (E = 15 for each step) with those obtainable by conventional methods.

% ee of final product.	% Overall yield by conventional methods.[a]	% Overall yield by double kinetic resolution.
75	50	57
80	48	55
85	45	52
90	43	49
95	39	42
99	34	<1

[a] Non-selective hydrolysis of the recovered reactant from a kinetic resolution.

As can be seen from **Table 4**, this double kinetic resolution strategy shows a significant improvement in overall product yield for a range of enantiomeric excesses. However, since in both kinetic resolutions (used in this double kinetic resolution strategy) the product is required, there is a limitation to the maximum enantiomeric excess achievable.*

It should be noted that the only difference between non-selective hydrolysis of the recovered reactant from the first kinetic resolution and the double kinetic resolution strategy is the second step, in particular the same number of isolation and separation steps are involved. The theoretical benefits should therefore be realisable in practice.

3.3 Application of the Proposed Double Kinetic Resolution Strategy.

Calculations as shown in **Table 5** using the computer model (Appendix 1) indicated that, for a final product enantiomeric excess of 95% (when E = 15 for both kinetic resolutions), maximum yield using the double kinetic resolution strategy described above would be obtained by allowing the first kinetic resolution to run to 52% conversion and the second kinetic resolution to run to 81% conversion.

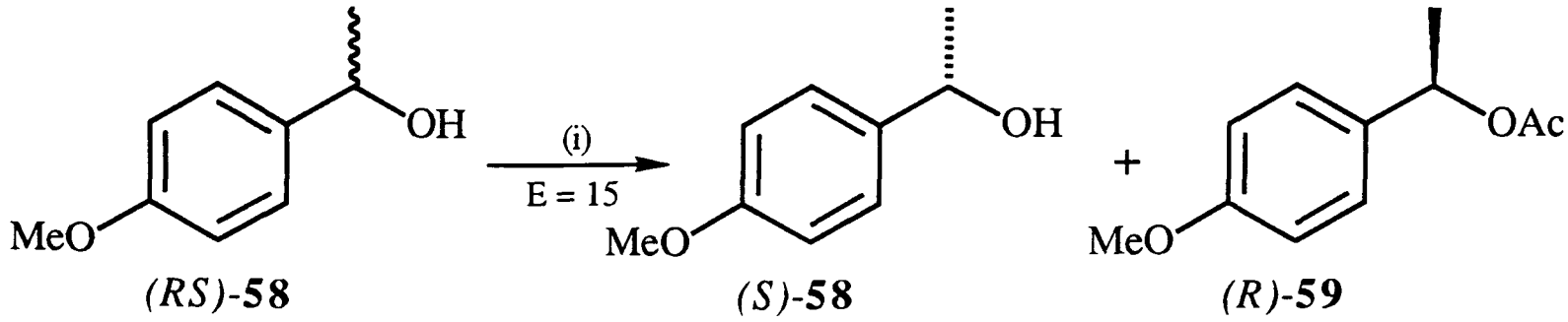
*The maximum enantiomeric excess achievable using this double kinetic resolution strategy can be calculated using the relationship: maximum product ee = $[(E_1 \times E_2)-1]/[(E_1 \times E_2)+1]$
(Where E_1 and E_2 are the stereoselectivity factors for the first and second kinetic resolutions respectively.)
Therefore in this case, maximum product ee = [(15 x 15)-1]/[(15 x 15)+1] = 99.1%.

Table 5 : Calculation of the % conversion required (in each kinetic resolution) to give the maximum possible overall yield of product with 95% ee by double kinetic resolution.

% Conversion in first kinetic resolution.	% ee of product from first kinetic resolution.	% Conversion in second kinetic resolution to give a product with 95% ee.	% Overall yield.
45	77.5	88	39.6
48	75.8	85	40.8
49	75.1	84	41.2
50	74.4	83	41.5
51	73.7	82	41.8
52	72.8	81	42.1
53	71.9	79	41.9
54	71.0	77	41.6
55	69.9	75	41.3

With this in mind, a double kinetic resolution using *(RS)*-1-(4-methoxy-phenyl)ethanol (**58**) was performed. In the first kinetic resolution lipase mediated esterification was performed (**Scheme 29**). The reaction was stopped after having proceeded to approximately the required (51%) conversion (conversion was monitored by ^{1}H NMR spectroscopy). Workup and flash chromatography enabled isolation of the recovered reactant [*(S)*-**58**] in 47% yield and the ester product [*(R)*-**59**] in 48% yield. The enantiomeric excess of the recovered reactant (**58**) was measured by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent: (+)-Eu(hfc)$_3$. Enantiomeric excess of the product (**59**) was measured by the same technique after chemical hydrolysis (potassium carbonate/methanol). The product (**59**) had an enantiomeric excess of 74% and the recovered reactant (**58**) had an enantiomeric excess of 76%.

Scheme 29 : First kinetic resolution.



(RS)-**58**

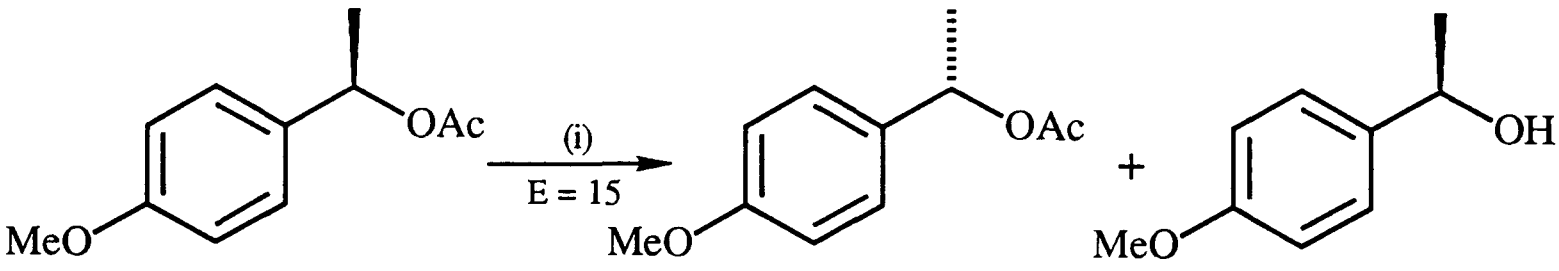
(S)-**58**
76% ee
47% yield

(R)-**59**
74% ee
48% yield

(i) PFL, vinyl acetate, CH_2Cl_2. 51% conversion.

The product [*(R)*-**59**] (74% ee) from the first kinetic resolution was used as the starting material in the second kinetic resolution in which PFL mediated hydrolysis was performed (**Scheme 30**). The extent of the reaction was monitored by the amount of 1N sodium hydroxide dispensed by the autotitrator in order to maintain the reaction mixture at pH 7. At the appropriate conversion (82%) the reaction was halted. Workup followed by flash chromatography gave recovered reactant [*(S)*-**59**] in 12% yield with an enantiomeric excess of 27% (model predicted 22%) and the required product [*(R)*-**58**] in 77% yield with an enantiomeric excess of >95%.

Scheme 30 : Second kinetic resolution.



(R)-**59**
74% ee

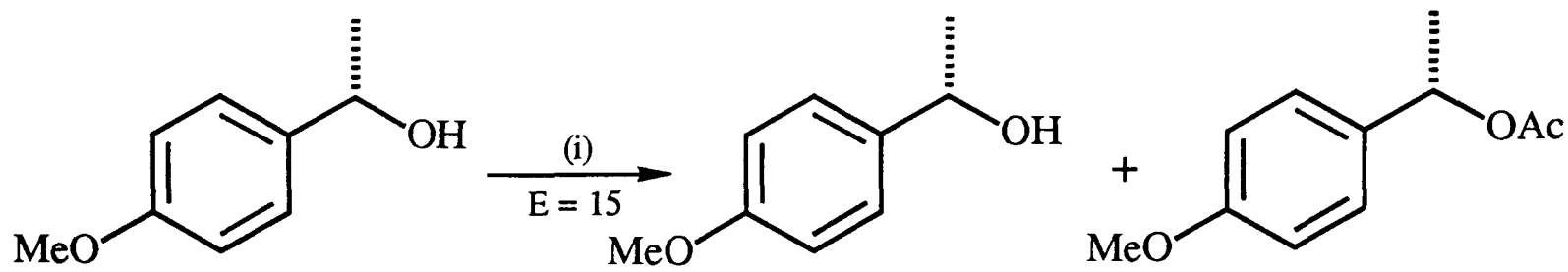
(i) PFL, pH 7 buffer. 82% conversion.

(S)-**59**
27% ee
12% yield

(R)-**58**
>95% ee
77% yield
37% overall yield

The recovered reactant [*(S)*-**58**] (76% ee) from the first kinetic resolution was treated again with PFL and vinyl acetate in dichloromethane. The reaction was stopped after 20% conversion. After workup and flash chromatography, *(S)*-**58** was obtained with an enantiomeric excess of >95% and a yield of 70% (**Scheme 31**).

Scheme 31 : Preparation of *(S)*-**58** (>95% ee) by treating the recovered reactant from the first kinetic resolution with PFL and vinyl acetate in dichloromethane.



(S)-**58**
76% ee

(i) PFL, vinyl acetate, CH_2Cl_2. 20% convn.

(S)-**58**
>95% ee
70% yield
33% overall yield

(S)-**59**
7% ee
15% yield

3.4 Consideration of this Double Kinetic Resolution Strategy for a Range of Stereoselectivity Factors.

Using data obtained from the computer model (Appendix 1) a series of plots was made for a range of stereoselectivity factors comparing the overall theoretical yields and product enantiomeric excesses obtainable using this double kinetic resolution strategy with those obtainable by conventional methods (**Figures 14** to **17**, see also **Figure 13**).

It is apparent from **Figures 14** to **17** that as the stereoselectivity factor increases, the benefits of this double kinetic resolution strategy diminish. **Figures 14** to **17** were prepared using the same method as used for **Figure 13** (see Appendix 4).

Figure 14 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy.

(E = 3 for each step: maximum product ee = 80.0%).

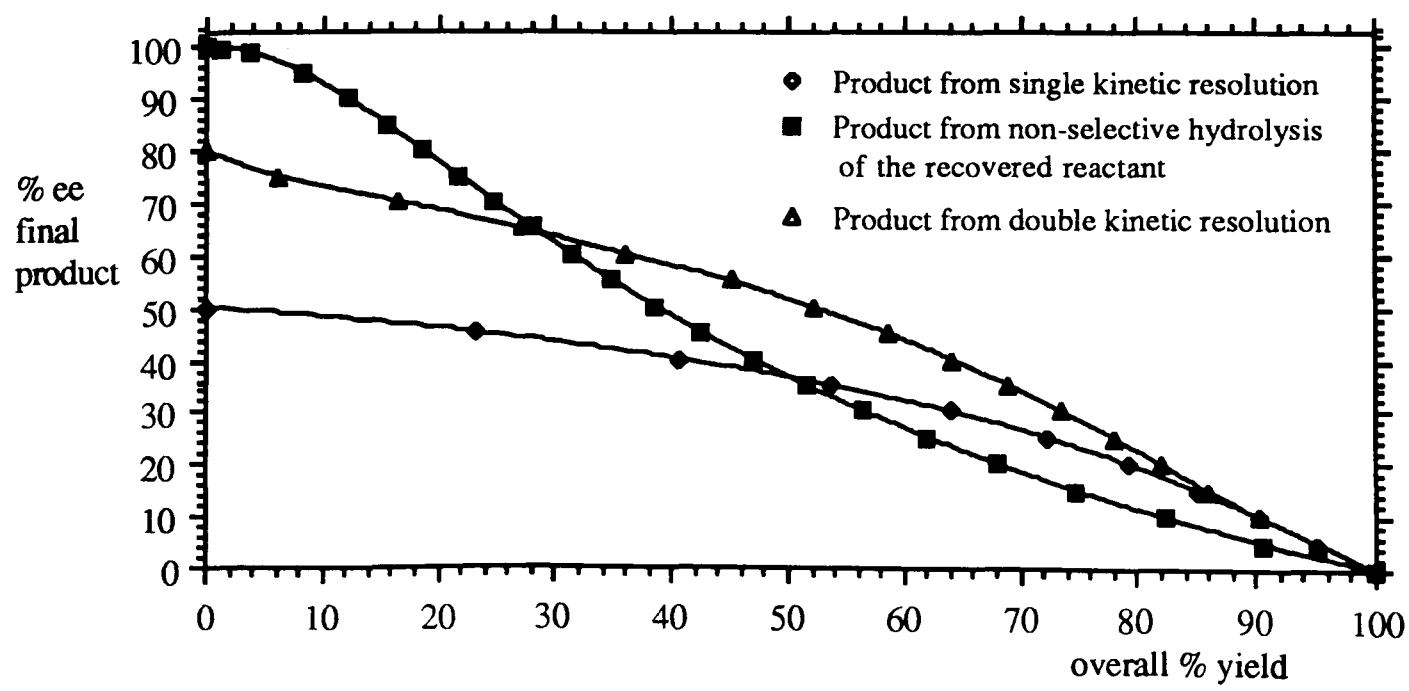


Figure 15 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 6 for each step: maximum product ee = 94.6%).

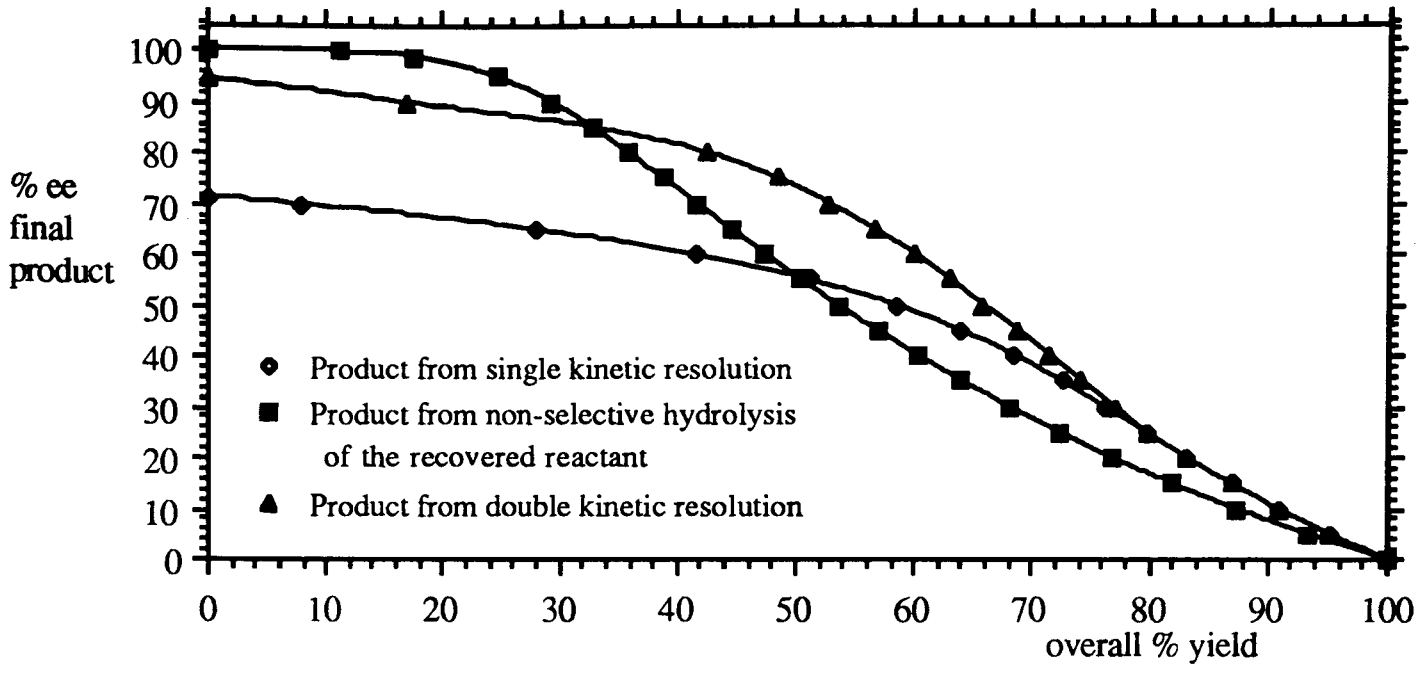


Figure 16 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 10 for each step: maximum product ee = 98.0%).

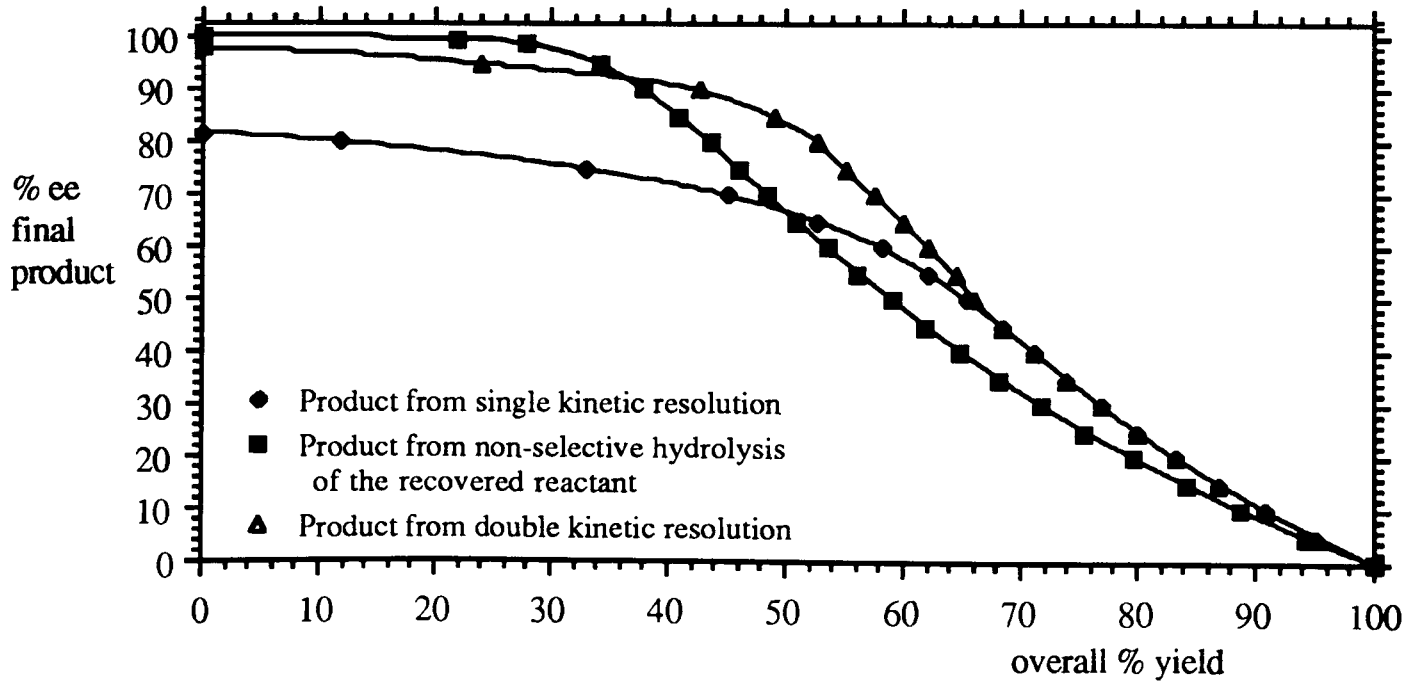
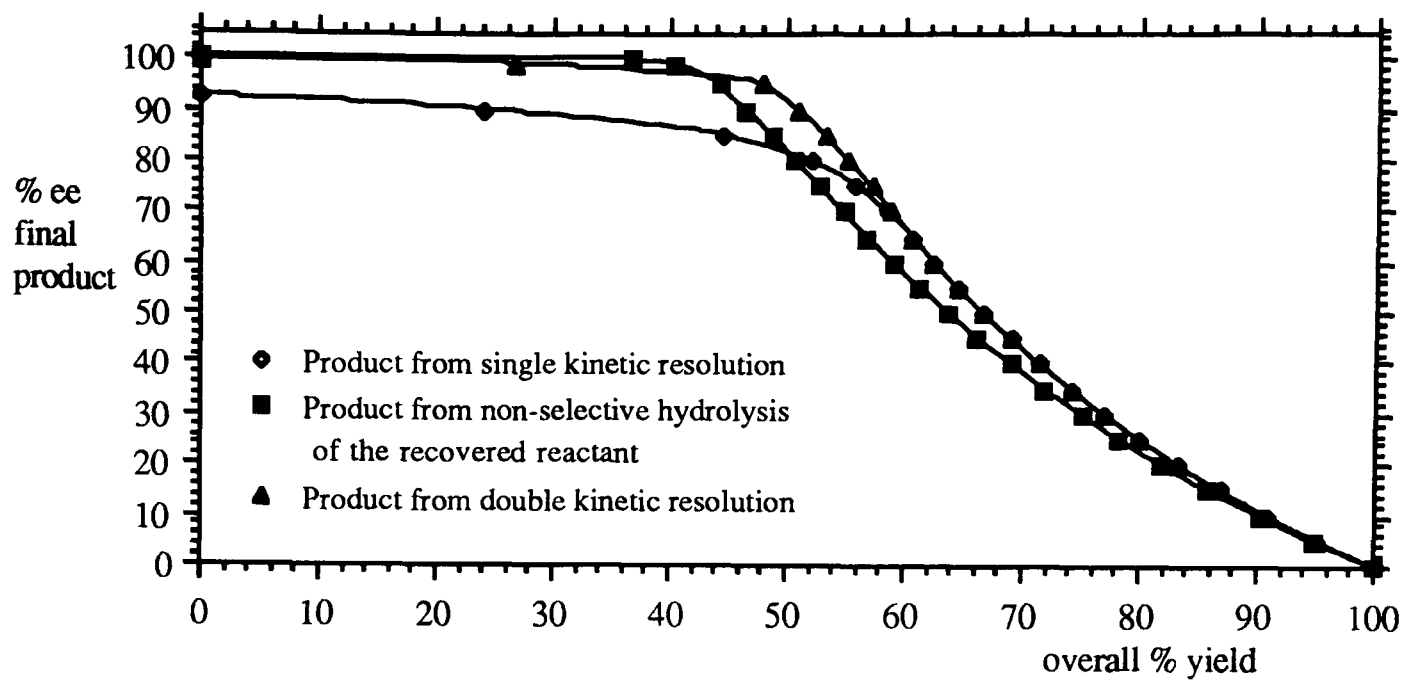


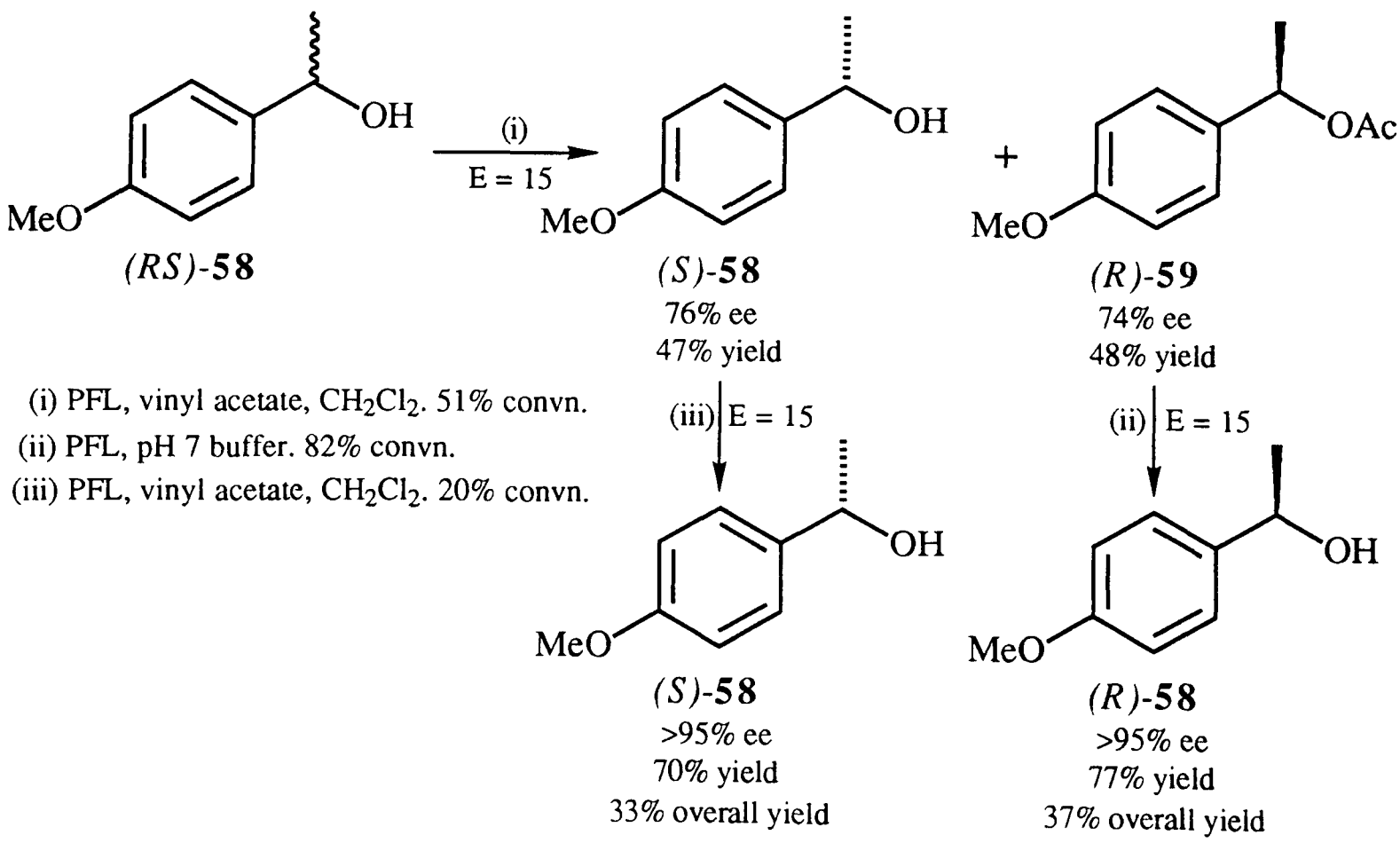
Figure 17 : Comparison of enantiomeric excesses and yields obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy. (E = 25 for each step: maximum product ee = 99.7%).



3.5 Summary and Conclusion.

Use of a double kinetic resolution strategy where the product from the first kinetic resolution was used as the starting material in a second kinetic resolution has been shown to enable formation of product with enhanced overall yield.

Scheme 32 : Summary.



The main criterion required for this double kinetic resolution strategy to be feasible is that suitable homochiral catalysts or reagents are available for each kinetic resolution.

For a comparison of this double kinetic resolution strategy with a number of other double kinetic resolution strategies see Appendix 2.

Chapter 4

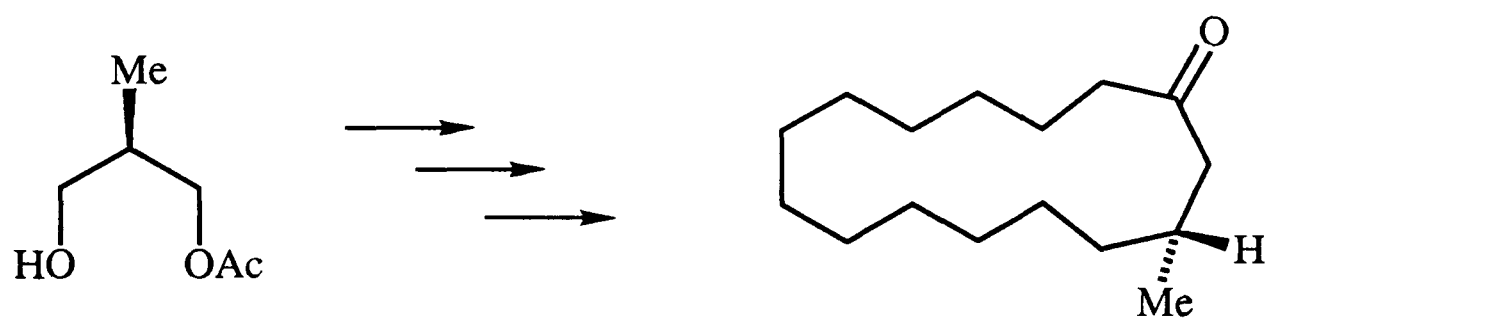
Preparation of Homochiral 2-substituted mono-protected propan-1,3-diol derivatives *via* the Combination of an Asymmetric Synthesis and a Kinetic Resolution.

4.1 Uses of Homochiral 2-substituted propan-1,3-diol derivatives.

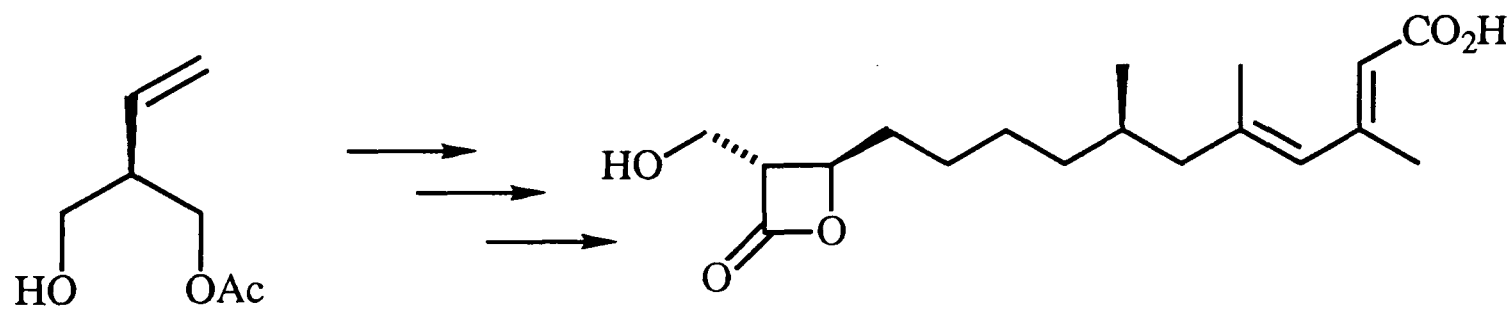
Homochiral 2-substituted propan-1,3-diol derivatives have been shown to be very useful chiral building blocks for the synthesis of biologically active compounds.

For example Sakai *et al.* made use of the *(R)*-monoacetate of 2-methylpropan-1,3-diol (**60**) in the preparation of (-)-muscone (**61**) as shown in **Scheme 33**.[55] *(R)*-2-Hydroxymethyl-3-butenyl acetate (**62**) has been used as a chiral precursor by Mori *et al.* in the synthesis of the antibiotic 1233A (**63**).[56] The microbial growth factor (-)-A-factor (**65**) was prepared by Sih *et al.* from *(S)*-3-hydroxy-2-(prop-2-ene)propyl acetate (**64**).[57]

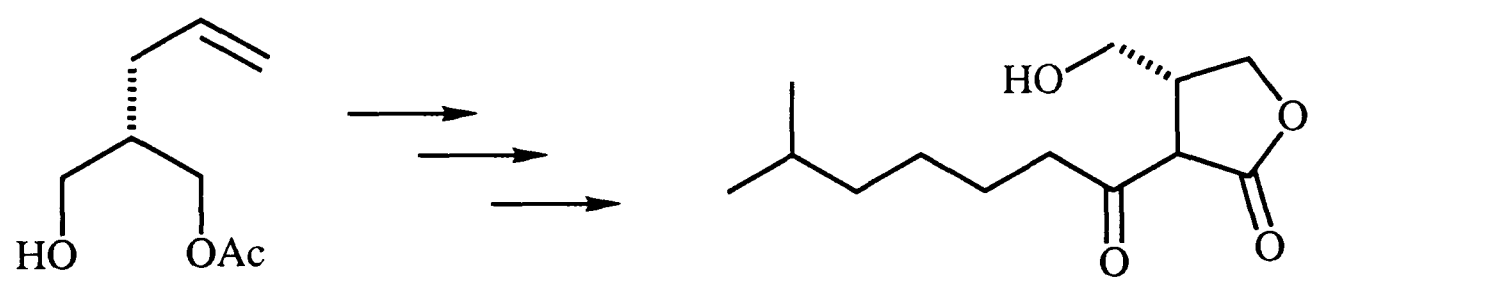
Scheme 33 : Use of homochiral propan-1,3-diol derivatives as chiral building blocks.



(R)-(+)-**60** *(R)*-(-)-muscone **61**



(R)-(+)-**62** 1233A **63**



(S)-(-)-**64** (-)-A-factor **65**

There are many other examples in the chemical literature where homochiral propan-1,3-diol derivatives have been used as chiral building blocks. These include the synthesis

of both enantiomers of paraconic acid,[58] preparation of various renin inhibitors,[59] and synthesis of the β-blocker *(S)*-propranolol.[60]

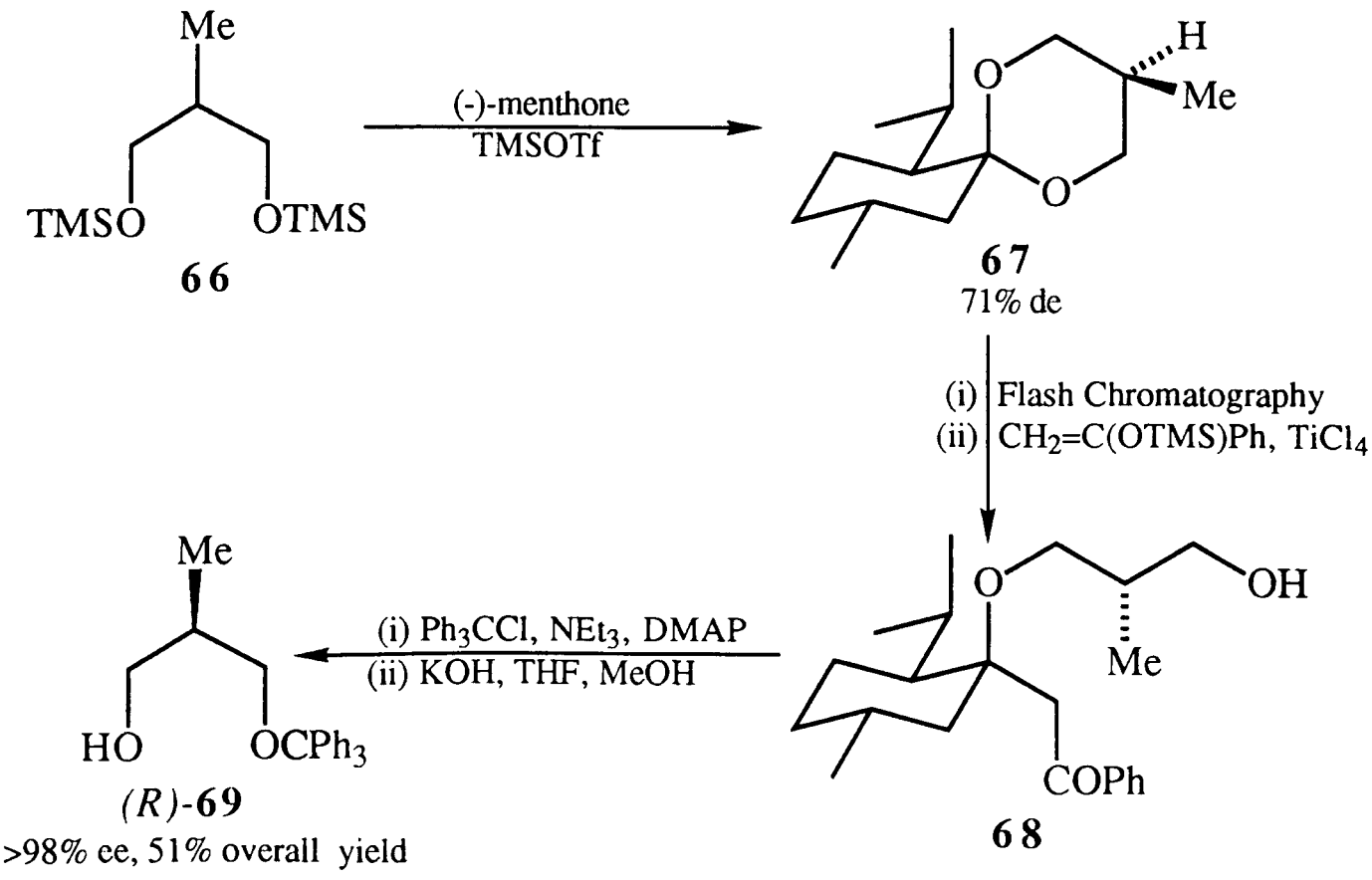
4.2 Preparation of Homochiral 2-substituted propan-1,3-diol derivatives.

The wide utility of homochiral propan-1,3-diol derivatives has led to a great interest in their preparation. Methods reported in the chemical literature for their synthesis fall into two distinct categories.

4.2.1 Chemical Methods.

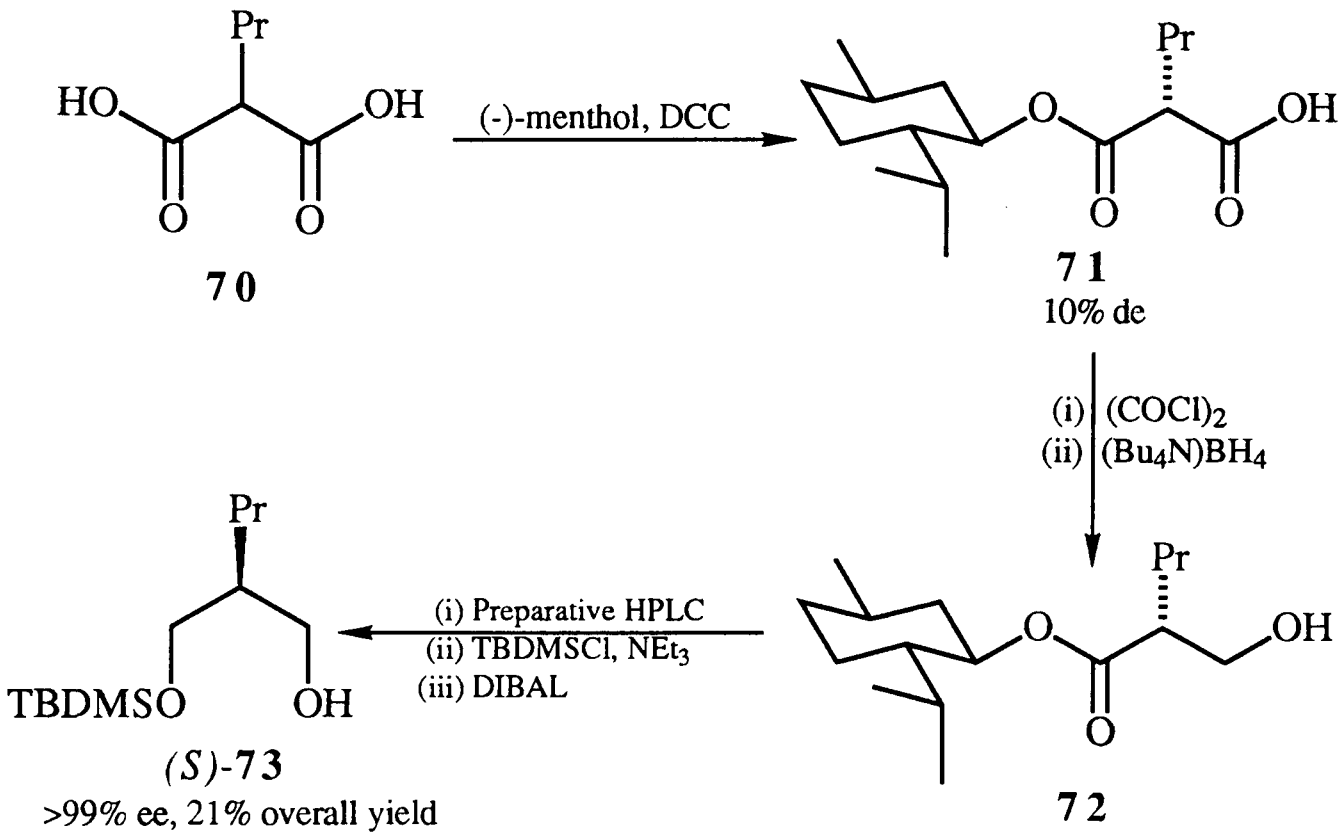
Treatment of 1,3-di(trimethylsilyloxy)propane (**66**) with (-)-menthone in the presence of a catalytic amount of trimethylsilyl triflate leads to formation of the spiroketal (**67**) with a diasteromeric excess of 71%. After separation of the diastereomers by flash chromatography, titanium tetrachloride promoted ring opening of **67** with the trimethylsilyl enol ether of acetophenone afforded the monoprotected diol (**68**) with a diastereomeric excess of >95%. Protection of the free hydroxyl group of **68** followed by removal of the neomenthyl group, under basic conditions, yields the 1,3 diol derivative [*(R)*-**69**] with an overall yield (from **66**) of 51% and with an enantiomeric excess of >98% (**Scheme 34**).[61]

Scheme 34 : Homochiral propan-1,3-diols *via* stereoselective opening of spiroketals.



Fukumoto *et al.* prepared homochiral propan-1,3-diol derivatives *via* the reaction of 2-substituted malonic acid derivatives (**70**) with (-)-menthol to form the malonic half ester (**71**) as shown in **Scheme 35**. Reduction of the acid chloride of **71** leads to formation of the hydroxy ester (**72**) as a 3 : 2 mixture of diastereomers. Separation of the diastereomers by preparative HPLC was followed by protection of the free hydroxyl group as its (*t*-butyl)dimethylsilyl ether, and reduction of the remaining ester group with diisobutyl aluminium hydride (DIBAL). Product (**73**) was obtained with an overall yield of 21% (from **70**) and with an enantiomeric excess of >99%.[62]

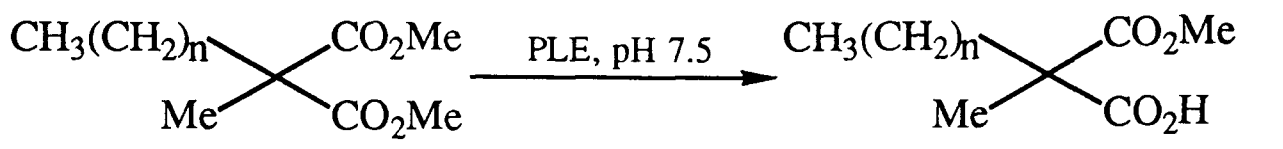
Scheme 35 : Homochiral propan-1,3-diols *via* preparation of menthyl half esters.



4.2.2 Enzymic Methods.

Enzymes have been used widely for the preparation of homochiral propan-1,3-diol derivatives. In many cases a prochiral substrate has been employed. For example pig liver esterase (PLE) catalyses the hydrolyses of a large number of dialkylated malonic esters (**74**). The reactions proceed with excellent yields to give products with good enantiomeric excesses as shown in **Scheme 36**.[63] Protection of the half esters (**75**) followed by reduction leads to formation of the required monoprotected propan-1,3-diol derivatives.

Scheme 36 : PLE mediated hydrolysis of dialkylated malonic esters.



n = 1 to 6

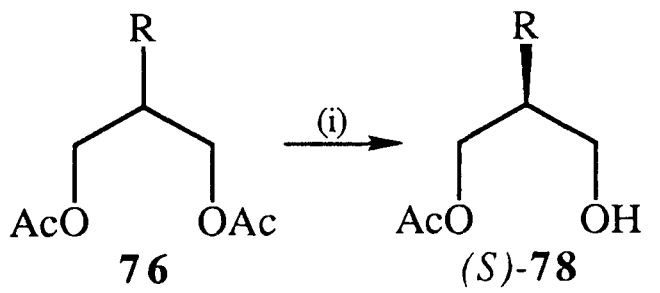
74

n = 1 to 3 : *(S)*. n = 4 to 6 : *(R)*.
73 - 88% ee, 90 - 98% yield

75

Prochiral 2-substituted propan-1,3-diols (**77**) and their diacetates (**76**) have also been used as substrates. Lipase mediated hydrolysis of the diacetates (**76**) in aqueous media or esterification of the diols (**77**) in organic media can lead to formation of the monoacetylated homochiral propan-1,3-diols (**78**) with excellent yields and enantiomeric excesses.[64] Ramos-Tombo *et al.* prepared both enantiomers of a number of 2-substituted propan-1,3-diol monoacetates using pig pancreatic lipase (PPL).[65] Enantiomeric excess of the product depends on the substituent at the 2 position as shown in **Scheme 37**.

Scheme 37 : Use of prochiral diols and diacetates for the preparation of homochiral monoacetylated propan-1,3-diol derivatives.



76 *(S)*-**78**

77 *(R)*-**78**

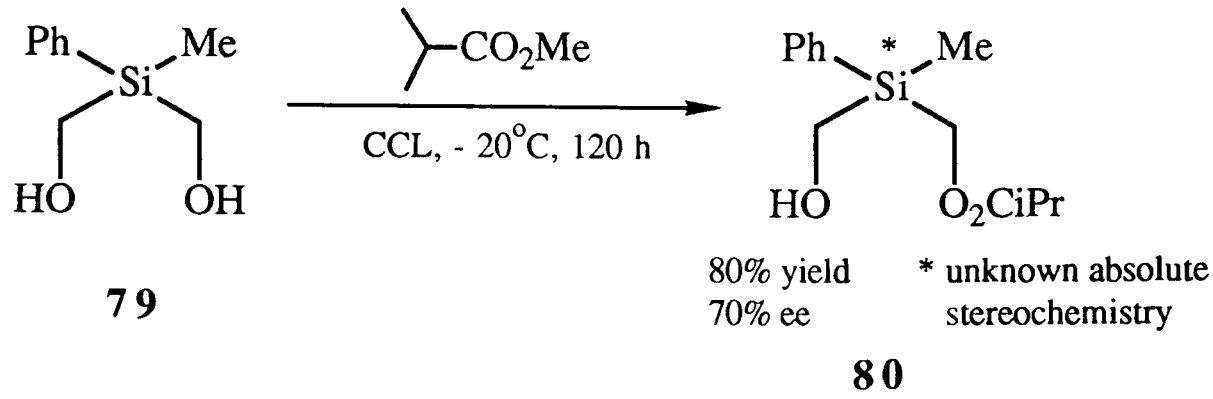
R	% ee	% yield
$CH_2CH_2CH=CH_2$	90	70
C_6H_5	92	98
$CH_2C_6H_5$	13	90
C_6H_{11}	58	90

R	% ee	% yield
$CH_2CH_2CH=CH_2$	>95	80
C_6H_5	>95	91
$CH_2C_6H_5$	61	65
C_6H_{11}	60	96

(i) PPL, pH 7.
(ii) PPL, methyl acetate.

Blanco *et al.* employed this methodology for the preparation of optically active monoacylated 2-sila-propan-1,3-diols (such as **79**) using *candida cylindracea* lipase (CCL) as shown in **Scheme 38.**[66]

Scheme 38 : Preparation of optically active monoacylated 2-sila-propan-1,3-diol derivatives *via* enzymic esterification.

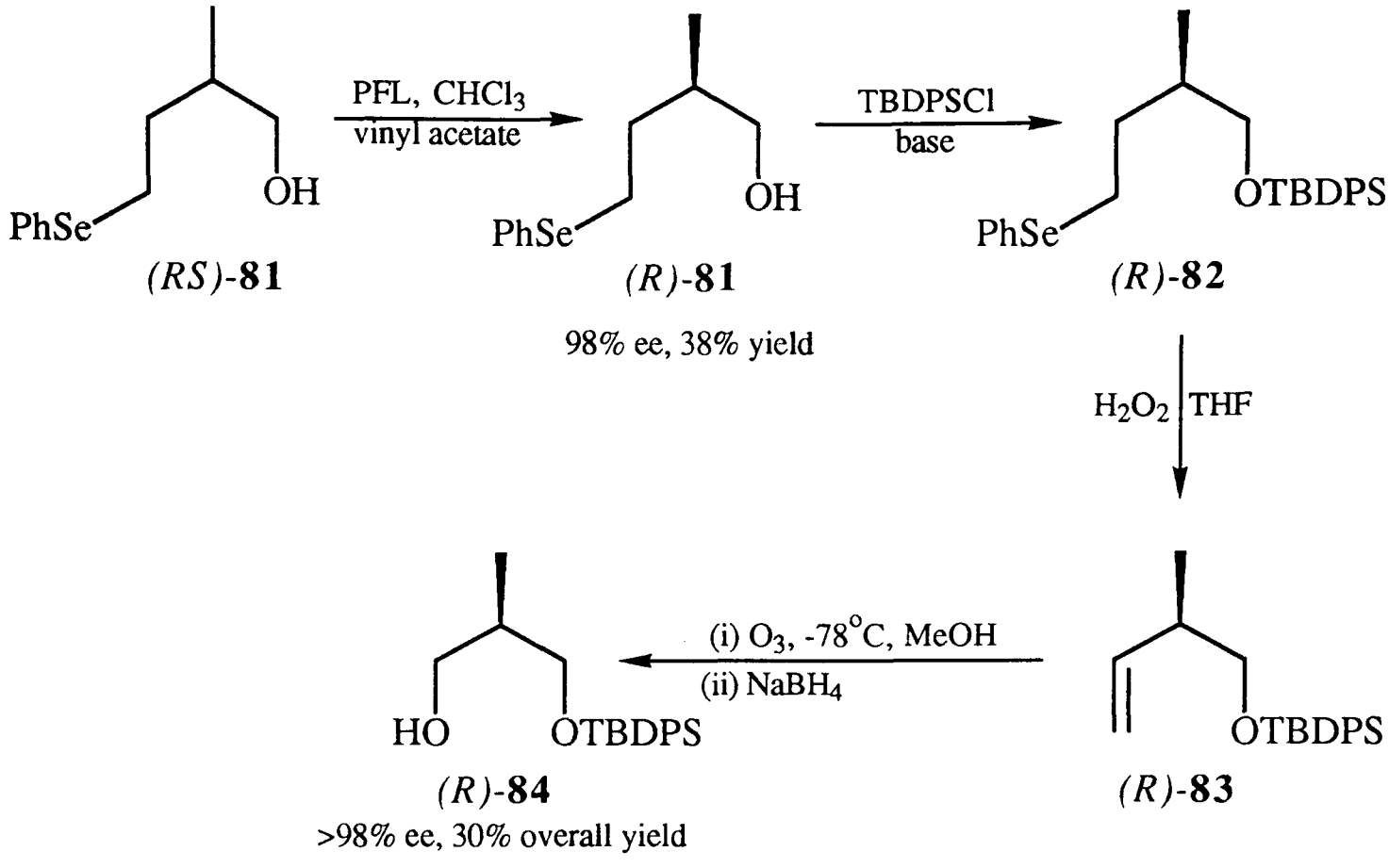


79 **80**

For prochiral substrates, product enantiomeric excess is governed by the ratio of the rates of formation of the two product enantiomers and is independent of the extent of reaction. For example, if a product enantiomeric excess of at least 95% is required, the ratio of the rates of formation of the two product enantiomers must be greater than 39. When the ratio of rates is not so high, use of a prochiral substrate does not allow high product enantiomeric excesses to be obtained.

One solution to this problem is to perform a kinetic resolution on a suitable racemic substrate.[67] This method was used by Santaniello *et al.* (**Scheme 39**).[68] Kinetic resolution of 4-phenylselenyl-2-methylbutan-1-ol (**81**) with *pseudomonas fluorescens* lipase (PFL) affords recovered *(R)*-**81** in 38% yield and with an enantiomeric excess of 98%. Protection of **81** as the silyl ether (**82**), followed by oxidative elimination of the phenylselenyl group leads to formation of the alkene (**83**). Ozonolysis and subsequent reduction of the intermediate ozonide produces the monoprotected propan-1,3-diol [*(R)*-**84**] with an overall yield of 30% (from **81**) and with an enantiomeric excess of >98%.

Scheme 39 : Synthesis of homochiral propan-1,3-diol derivatives *via* enzyme mediated kinetic resolution.

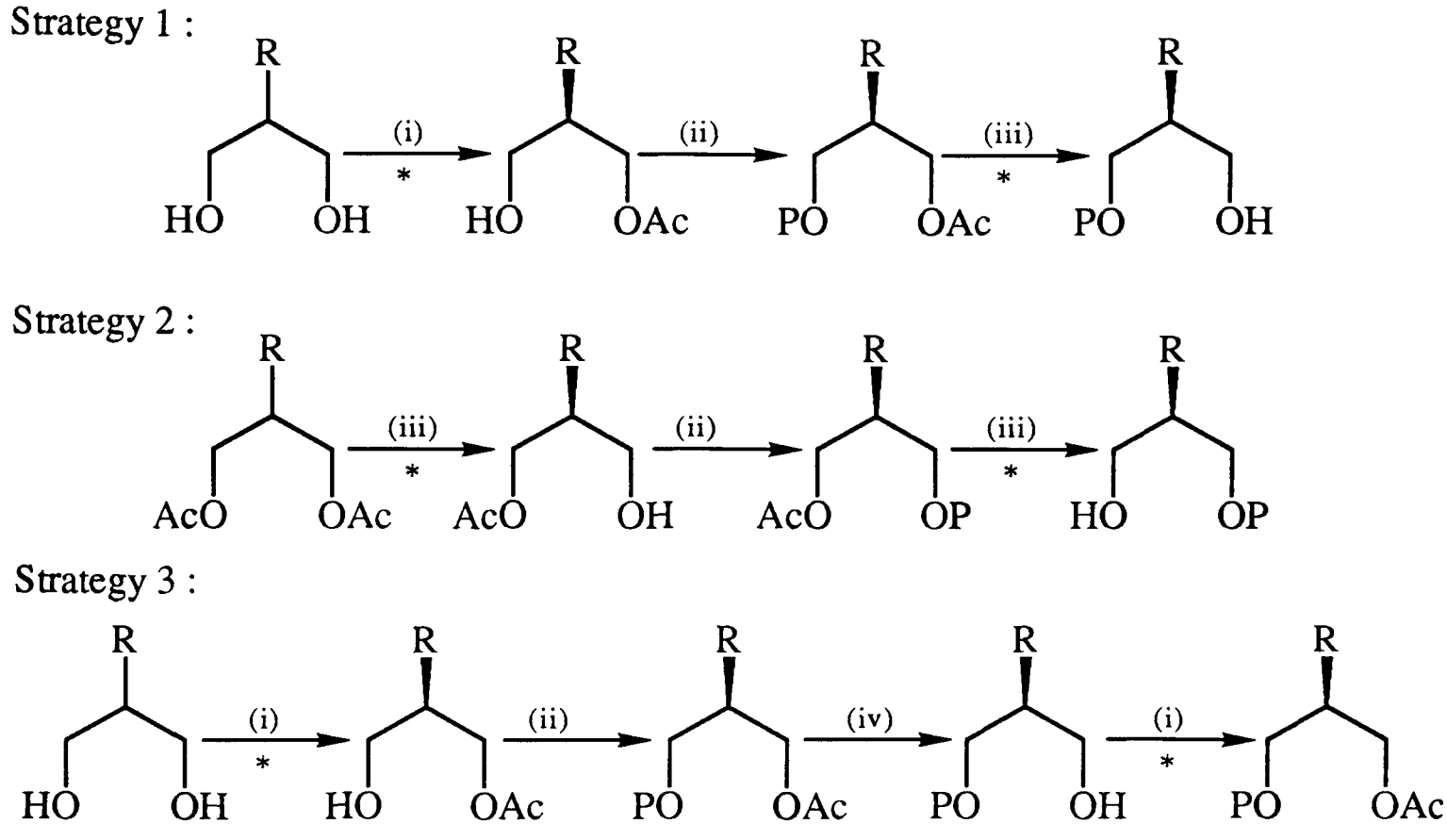


4.3 Proposed Combination of Asymmetric Synthesis and Kinetic Resolution for the Preparation of Homochiral propan-1,3-diol derivatives.

If the enzymic methods for the preparation of homochiral propan-1,3-diol derivatives are considered, there are two different approaches, both of which have their limitations. Use of a prochiral starting material leads to high product yields, however as stated previously, the enantiomeric excess of the product is limited by the ratio of the rates of formation of the two product enantiomers. In contrast, kinetic resolution of a suitable monoprotected propan-1,3-diol does enable high enantiomeric excesses to be obtained, however as with all conventional kinetic resolutions, the maximum yield is limited to 50%.

It was envisaged that if the two processes could be combined it would enable formation of the required monoprotected propan-1,3-diol derivatives with improved yields and enantiomeric excesses. A number of different strategies for combining the two processes are possible. **Scheme 40** shows the strategies considered.

Scheme 40 : Strategies considered for the preparation of homochiral propan-1,3-diols.



(i) Lipase, acyl donor, organic solvent. (ii) Protect free hydroxyl. P - protecting group
(iii) Lipase, aqueous media. (iv) K_2CO_3, MeOH. * - enantioselective reaction

In strategy 1 a prochiral diol is enantioselectively acetylated, and after protection of the free hydroxyl of the monoacetate, enzymic hydrolysis is performed to give the required product.

Strategy 2 uses a prochiral diacetate as starting material. Here, the first step is an enzymic hydrolysis to give a monoacetate, again protection of the monoacetate is followed by enzymic hydrolysis (as in strategy 1) to yield the required product.

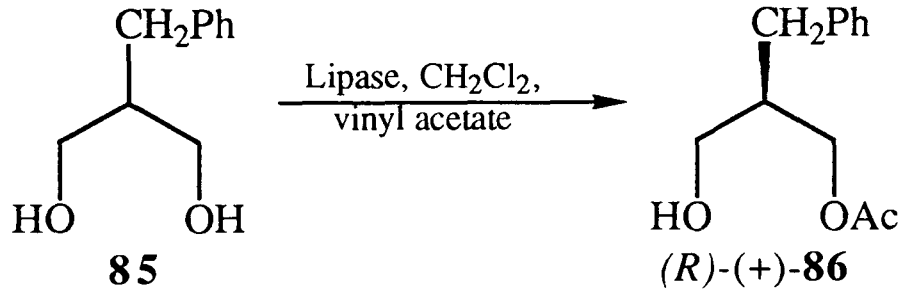
Strategy 3 is identical to strategy 1 except that instead of using an enzymic hydrolysis as the second enantioselective reaction, an enzymic acetylation is employed. This strategy was considered because it is frequently found to be the case that enzymic acetylation of a particular alcohol is more selective than enzymic hydrolysis of the corresponding acetate (see for example **Scheme 37**).

4.3.1 Identification of a Suitable Substrate and Exploratory Reactions.

A suitable substrate on which to demonstrate the proposed methodology was sought. An enantiomeric excess of 60 - 90% for the intermediate monoacetate (formed in the first enantioselective reaction) would be ideal.

Acetylation of 2-benzylpropan-1,3-diol (**85**) with a number of different lipases, using vinyl acetate as the acyl donor, gave the monoacetate [*(R)*-**86**] as shown in **Scheme 41**. Product enantiomeric excess was estimated by measurement of the specific rotation and comparison with the literature value.[59a]

Scheme 41 : Enzymic esterification of 2-benzylpropan-1,3-diol (**85**).



85 *(R)*-(+)-**86**

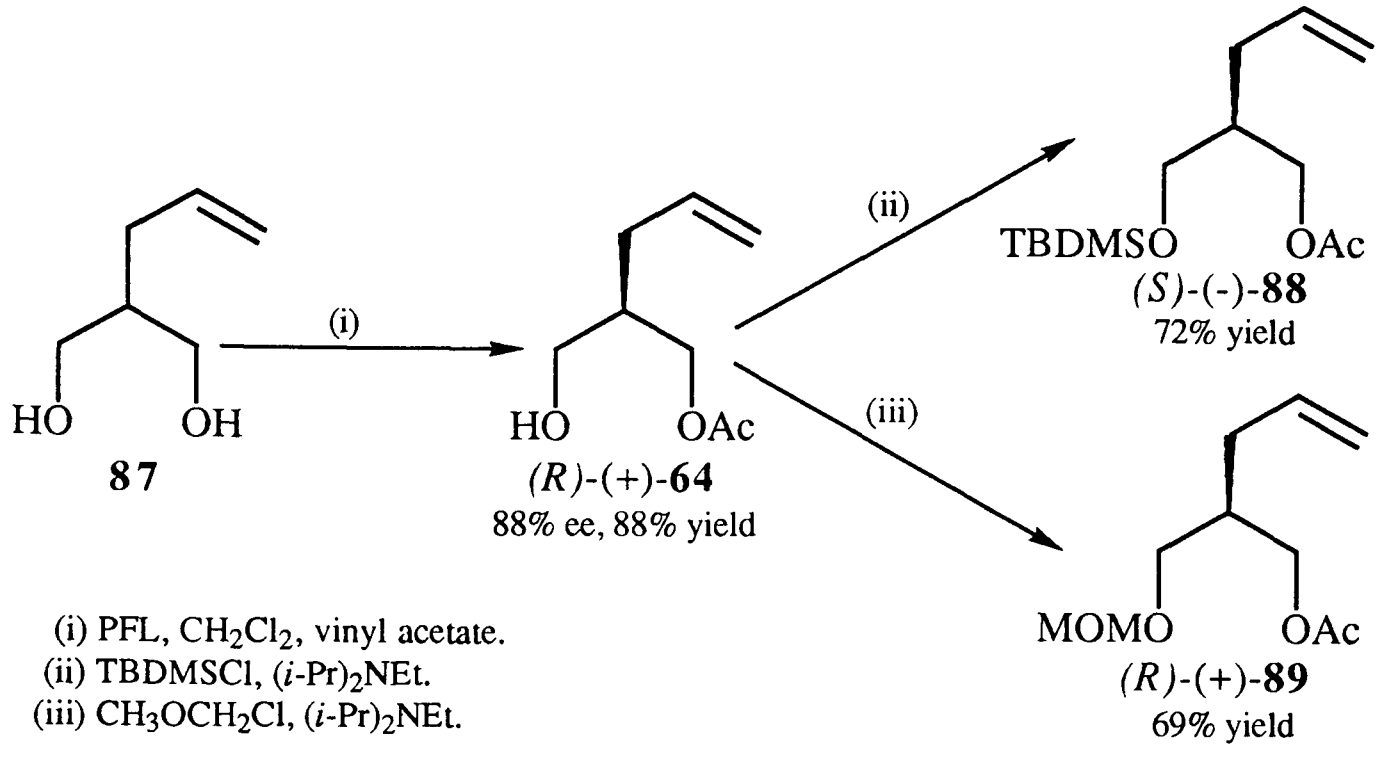
Lipase	% ec	% yield
PFL	>94	98
ANL	52	73
MJL	18	69
RAL	-	no reaction

The enantiomeric excess of the product obtained from the PFL mediated reaction was too high to be of use in demonstrating the proposed methodology. *Aspergillus niger* lipase (ANL) and *mucor javanicus* lipase (MJL) led to products with low enantiomeric excesses. With *rhizopus arrhizus* lipase (RAL) no product was formed. Therefore, **85** was not suitable and a different substrate was tried.

2-(Prop-2-ene)propan-1,3-diol (**87**) undergoes acetylation with PFL, using vinyl acetate as the acyl donor, to give the *(R)*-monoacetate (**64**) in 88% yield and with an enantiomeric excess of 88% (by comparison with the literature rotation[69]), and therefore appeared to be an ideal substrate (**Scheme 42**). The free hydroxyl group of *(R)*-**64** was protected, firstly as its (*t*-butyl)dimethylsilyl ether to give **88** in 72% yield and secondly as its methoxymethyl ether to give **89** in 69% yield. Both **88** and **89** were fully characterised. Since **88** and **89** have no published specific rotation a method for measuring their enantiomeric excesses was required. Hydrolysis of **88** and **89** followed by preparation of Mosher's esters[46] and subsequent analysis by ^{19}F NMR spectroscopy; ^{1}H NMR spectroscopy or HPLC did not work. Use of a number of chiral shift reagents

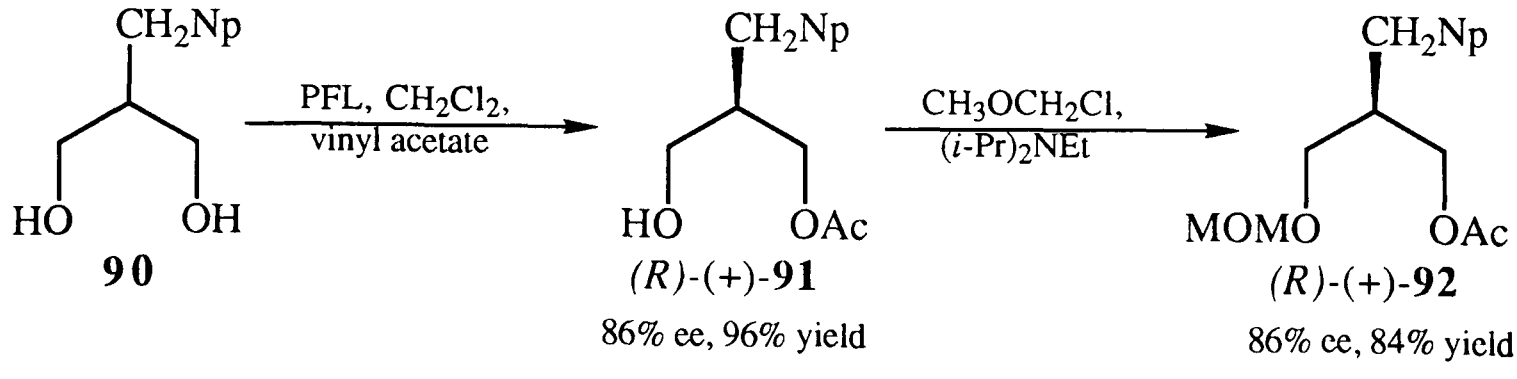
also proved unsuccessful. Without a method for measuring the enantiomeric excess of the intermediate (**88** or **89**) this substrate (**87**) could not be used, as it was important to be sure that no racemisation had occurred during the protection step.

Scheme 42 : PFL mediated esterification of 2-(prop-2-ene)propan-1,3-diol (**87**).



PFL mediated esterification of 2-(1-methylnaphthyl)propan-1,3-diol (**90**) was performed as shown in **Scheme 43**. The monoacetylated product [*(R)*-**91**] (which was fully characterised) was formed in 96% yield and with an enantiomeric excess of 86%.[59a] Protection of **91** as its methoxymethyl ether led to formation of **92** (which was fully characterised) in 84% yield. Enantiomeric excess measurement of **92** also proved to be difficult. Fortunately, HPLC using a Chiracel OB column (which possesses a homochiral stationary phase) did enable accurate calculation of the enantiomeric excess of **92** and indicated that no racemisation had occurred during the protection step.

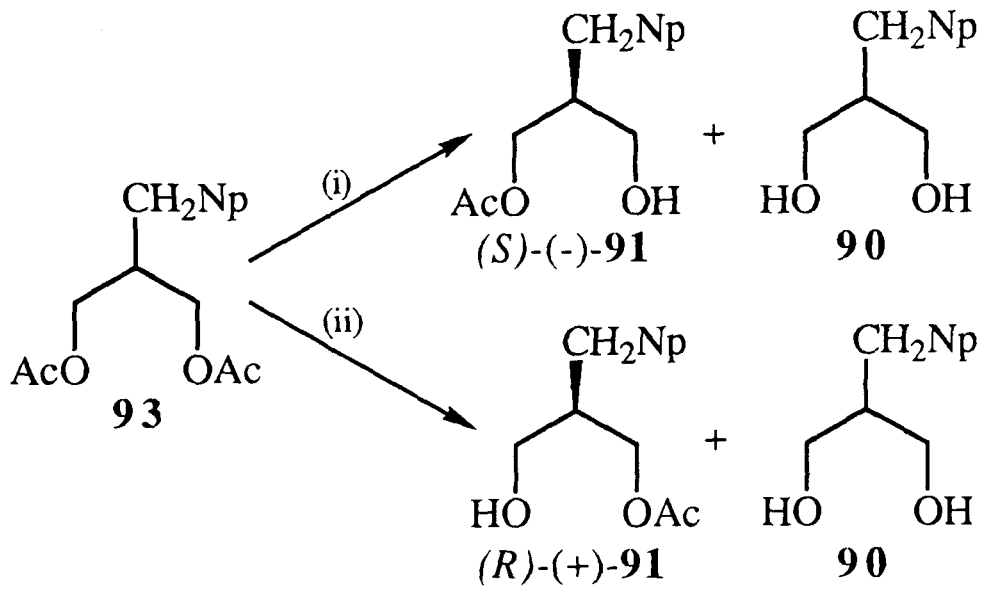
Scheme 43 : 2-(1-methylnaphthyl)propan-1,3-diol (**90**) as substrate.



It appeared that 2-(1-methylnaphthyl)propan-1,3-diol (**90**) would be a suitable substrate on which to demonstrate the proposed methodology. A number of exploratory reactions were performed in order to establish which of the strategies from **Scheme 40** would yield the best results.

Lipase mediated hydrolysis of 2-(1-methylnaphthyl)propan-1,3-diacetate (**93**) was performed and proceeded as shown in **Scheme 44**. With each of the three lipases screened, significant amounts of the corresponding diol (**90**) were formed; therefore in this case strategy 2 (**Scheme 40**) would not be suitable.

Scheme 44 : Enzymic hydrolysis of **93**

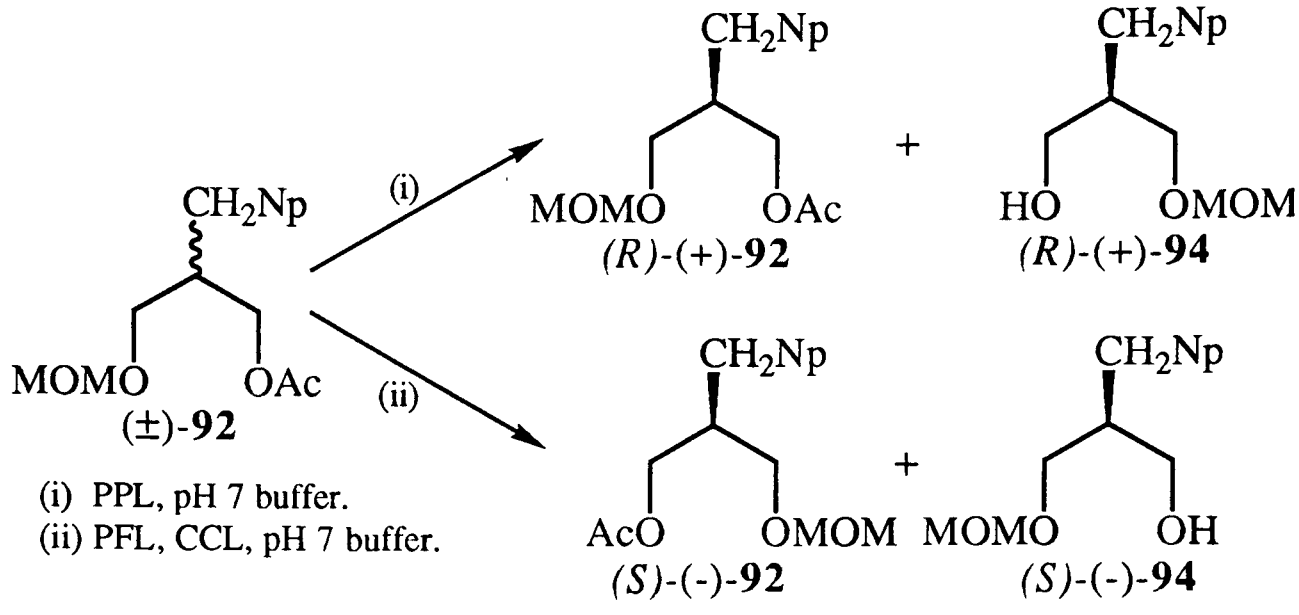


Lipase	**93 / 91 / 90**	% ee **91**
PFL	51 / 27 / 22	58
PPL	36 / 25 / 39	70
CCL	30 / 12 / 58	59

(i) PFL or CCL, pH 7 buffer.
(ii) PPL, pH 7 buffer.

With a view to employing strategy 1, kinetic resolution of (±)-**92** was performed with a number of different lipases and proceeded as shown in **Scheme 45** to give **94** (which was fully characterised). PFL mediated the hydrolysis of **92** with a stereoselectivity factor (E) ~ 5 and was the most selective of the enzymes tried.

Scheme 45 : Enzymic hydrolysis of (±)-**92**.

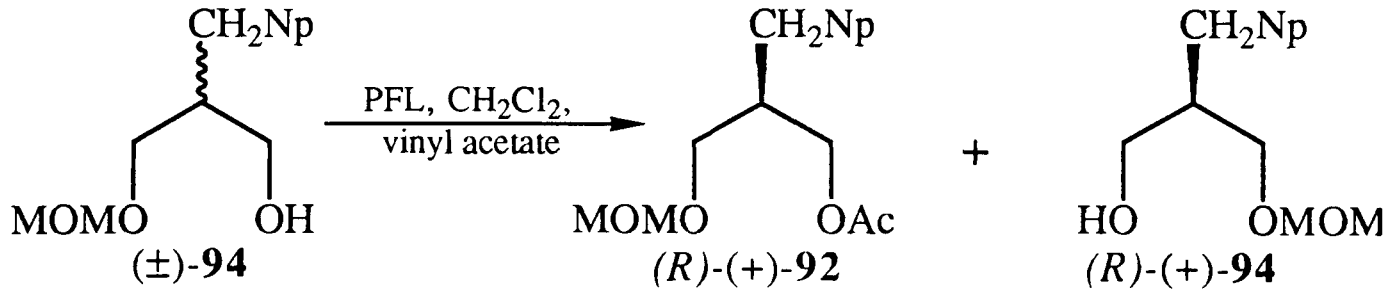


Lipase	% convn	% ee **92**	% ee **94**	E_R	E_P
PFL	38	32	55	4.4	4.7
PPL	45	19	10	1.9	1.3
CCL	49	24	19	2.1	1.7

E_R : Stereoselectivity factor with respect to reactant
E_P : Stereoselectivity factor with respect to product

With a view to employing strategy 3, PFL mediated acetylation of (±)-**94** was performed. This kinetic resolution proceeded with E ~ 2 (**Scheme 46**) and thus indicated that strategy 1 (E ~ 5) would be more effective (in this case) than strategy 3.

Scheme 46 : PFL mediated acetylation of (±)-**94**.



% convn	% ee **94**	% ee **92**	E_R	E_P
33	14	29	2.0	2.1

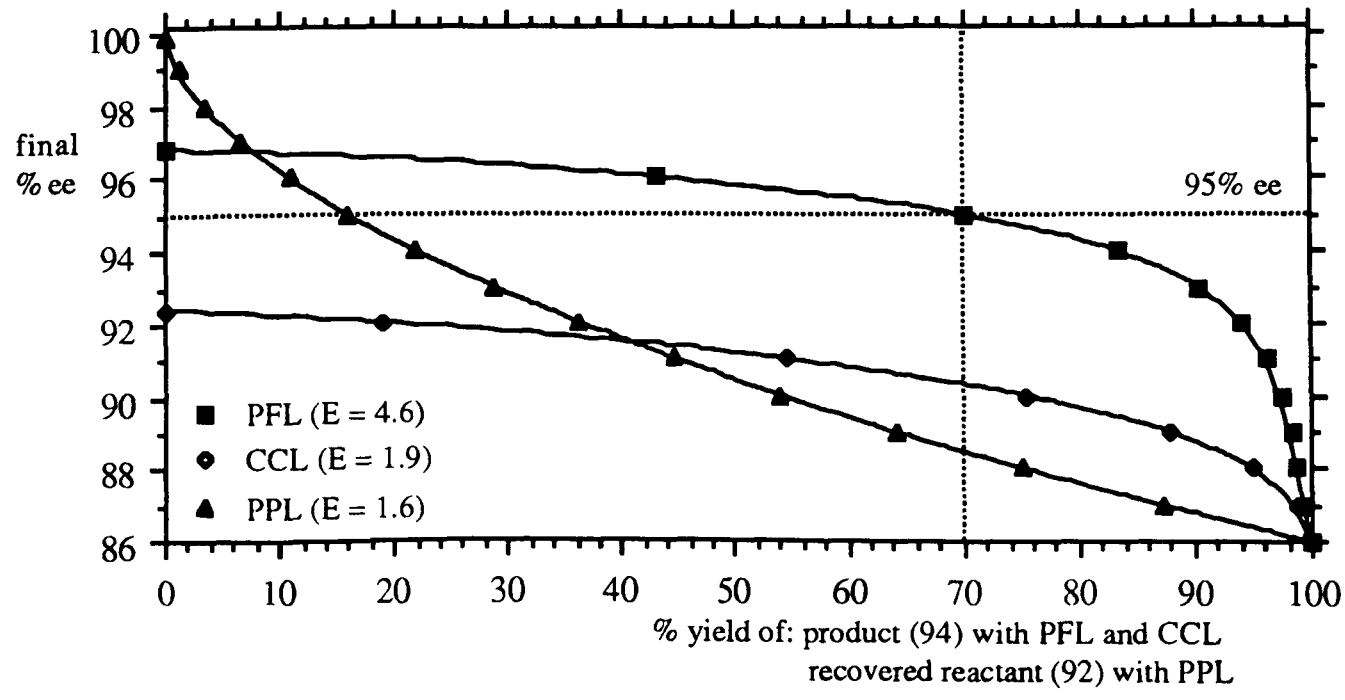
The exploratory reactions indicated that the proposed methodology could be demonstrated using strategy 1 (**Scheme 40**) with 2-(1-methylnaphthyl)propan-1,3-diol (**90**) as substrate.

4.4 Application of the Proposed Strategy.

The first step in the process was the enzymic esterification of **90** using PFL to give the monoacetate [*(R)*-(+)-**91**]. This was then protected to give *(R)*-(+)-**92** with an enantiomeric excess of 86% (**Scheme 43**). From the experiments performed in **Scheme 45** there was a choice of which enzyme to use for the hydrolysis step. With PFL and CCL, the faster reacting enantiomer of **92** is the *R* enantiomer. Since the intermediate (**92**) (obtained by PFL mediated esterification followed by protection) is enriched in the *R* enantiomer, use of PFL or CCL in the hydrolysis step would lead to formation of product (**94**) with enhanced enantiomeric excess (see Section 1.4.5.1). With PPL, the faster reacting enantiomer of **92** is the *S* enantiomer. Therefore if PPL were used in the hydrolysis step it would lead to recovered reactant (**92**) (rather than product) with enhanced enantiomeric excess (see Section 1.4.5.2).

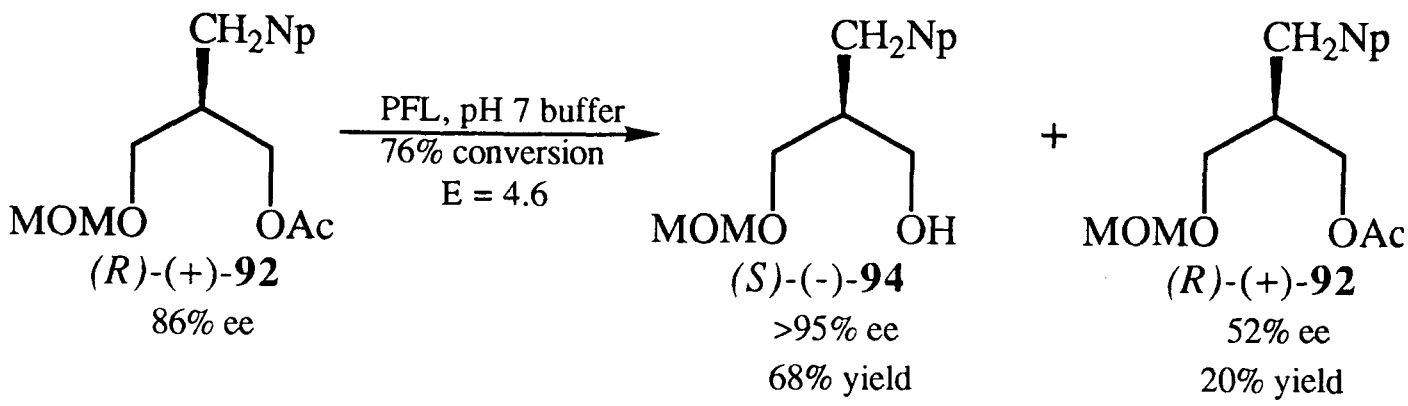
Use of the computer model (Appendix 1) enabled a plot of % yield against % enantiomeric excess (of product [**94**] or recovered reactant [**92**], depending on which lipase was used in the kinetic resolution) to be made (**Figure 18**). This indicated that for a final enantiomeric excess of 95%, maximum yield would be obtained using PFL in the hydrolysis step (rather than CCL or PPL) and by allowing the reaction to run to 70% conversion.

Figure 18 : Plot of % yield versus % enantiomeric excess of product (**94**) (in the case of PFL and CCL) or % enantiomeric excess of recovered reactant (**92**) (in the case of PPL) obtainable by hydrolysis of *(R)*-(+)-**92** (86% ee) with various lipases.



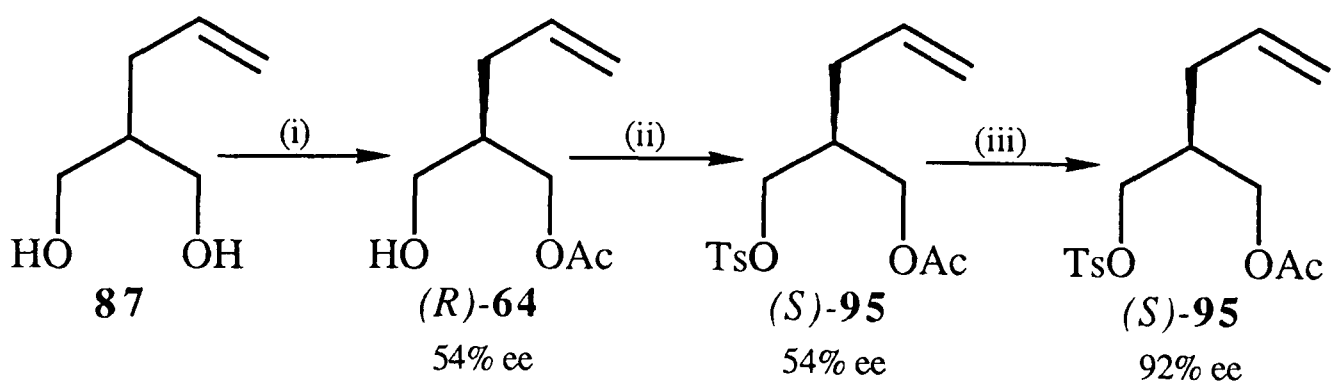
Therefore, to complete the two step process, PFL mediated hydrolysis of *(R)*-(+)-**92** (86% ee) was performed as shown in **Scheme 47**. After 76% conversion, recovered starting material *(R)*-(+)-**92** was obtained in 20% yield and with an enantiomeric excess of 52% (model predicted 58%), and the required product *(S)*-(-)-**94** was obtained in 68% yield and with an enantiomeric excess of >95%.

Scheme 47 : PFL mediated hydrolysis of *(R)*-(+)-**92** (86% ee)



Shortly after the completion of this work Wong *et al.* demonstrated the use of a similar methodology in which the diol **87** was used as shown in **Scheme 48**.[35] Interestingly in the second step, it was the *R* enantiomer of **95** [i.e the minor enantiomer (see Section 1.4.5.2)] that reacted faster, therefore in this case recovered reactant (rather than product) was obtained with enhanced enantiomeric excess.

Scheme 48 : Two step process performed by Wong *et al.*

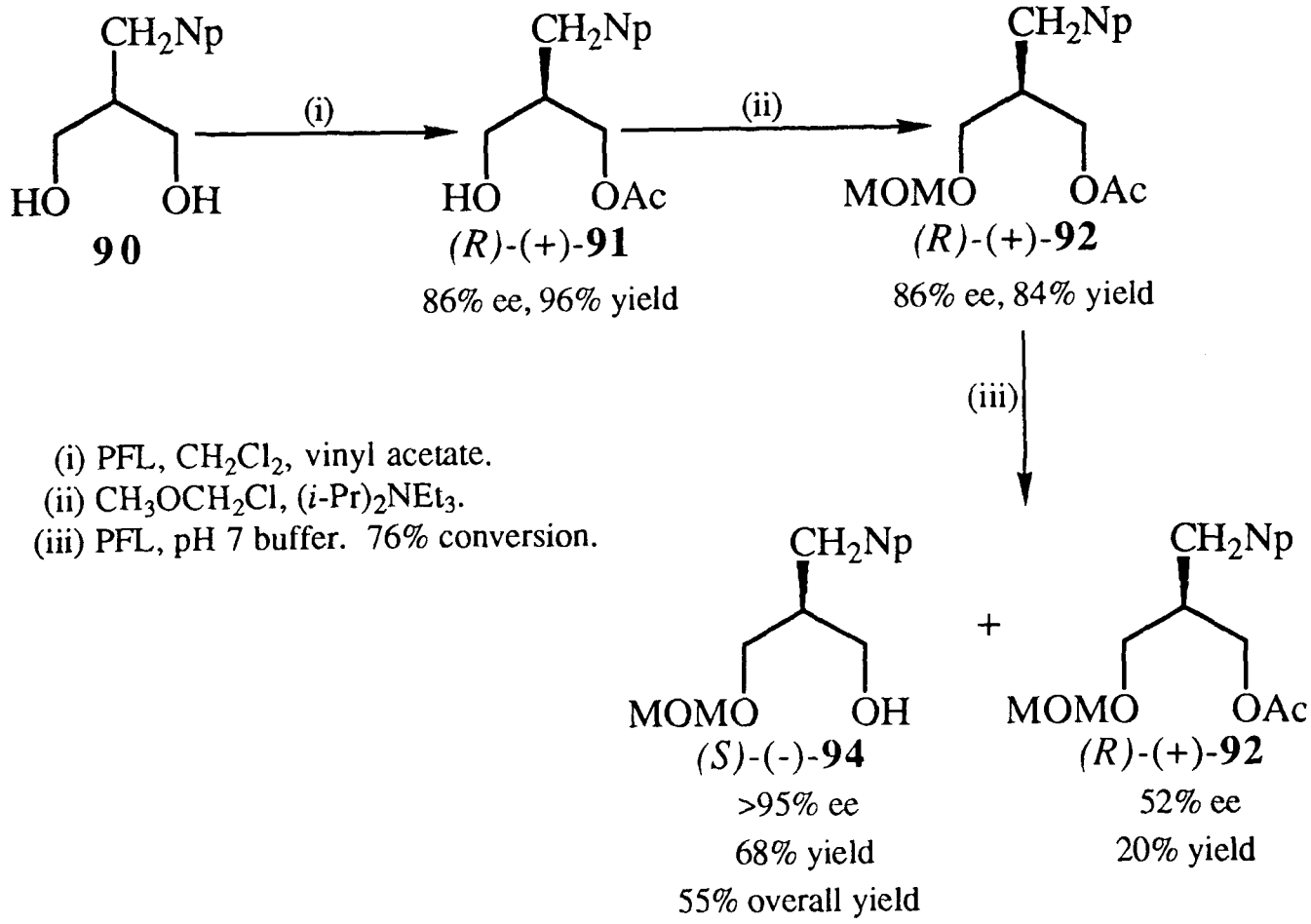


(i) PPL, vinyl acetate, $CHCl_3$. (ii) TsCl, pyridine. (iii) PPL, H_2O. 40% conversion.

4.5 Summary and Conclusion.

(S)-(-)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (**94**) was prepared by a technique involving enzymic esterification followed by kinetic resolution as shown in **Scheme 49**. The overall yield of *(S)*-(-)-**94** (>95% ee) obtained, starting from 2-(1-methylnaphthyl)propan-1,3-diol (**90**), was 55%. When compared with conventional methods; maximum enantiomeric excess using a prochiral substrate is only 86% (**Scheme 43**). For 95% ee, maximum yield obtainable by the kinetic resolution of *(RS)*-(±)-**92** (**Scheme 45**) is only 28%. Therefore this combination of an asymmetric synthesis and a kinetic resolution has been shown to enable significant improvements in yields and enantiomeric excesses for the preparation of homochiral monoprotected 2-substituted propan-1,3-diols.

Scheme 49 : Summary.



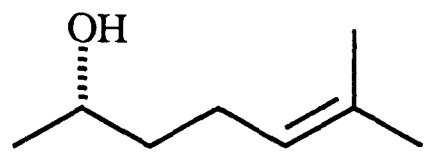
Chapter 5

Preparation of Sulcatol *via* the combination of an Asymmetric Synthesis and a Kinetic Resolution.

5.1 Biological Activity of Sulcatol.

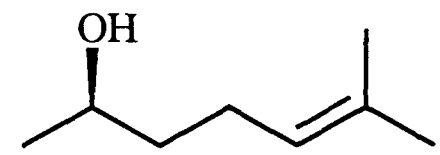
Sulcatol (6-methylhept-5-en-2-ol) (**96**) (**Figure 19**) is the aggregation pheromone of the ambrosia beetles: *Gnathotrichus sulcatus* and *Gnathotrichus retusus*. These beetles are economically important pests in felled and bucked timber. *Gnathotrichus retusus* is sensitive only to *(S)*-sulcatol (**96**) and its response is inhibited when *(R)*-sulcatol (**96**) is present.[70] Interestingly, *Gnathotrichus sulcatus* responds only when both *(R)* and *(S)*-sulcatol (**96**) are present, exposure to homochiral *(R)* or *(S)*-sulcatol (**96**) alone has no effect.[71] Indeed sulcatol (**96**) was first isolated from the boring dust of *Gnathotrichus sulcatus* and found to be present as a 65 : 35 mixture of *(S)* : *(R)* enantiomers.[72]

Figure 19 : 6-Methylhept-5-en-2-ol : Sulcatol (**96**).



(S)-(+)-sulcatol

(S)-**96**



(R)-(-)-sulcatol

(R)-**96**

5.2 Preparation of Sulcatol (96).

The biological activity of sulcatol (**96**) has led to the appearance of a number of methods for its preparation in homochiral form. As in the preparation of homochiral propan-1,3-diol derivatives (Chapter 4) the methods used fall into two distinct categories.

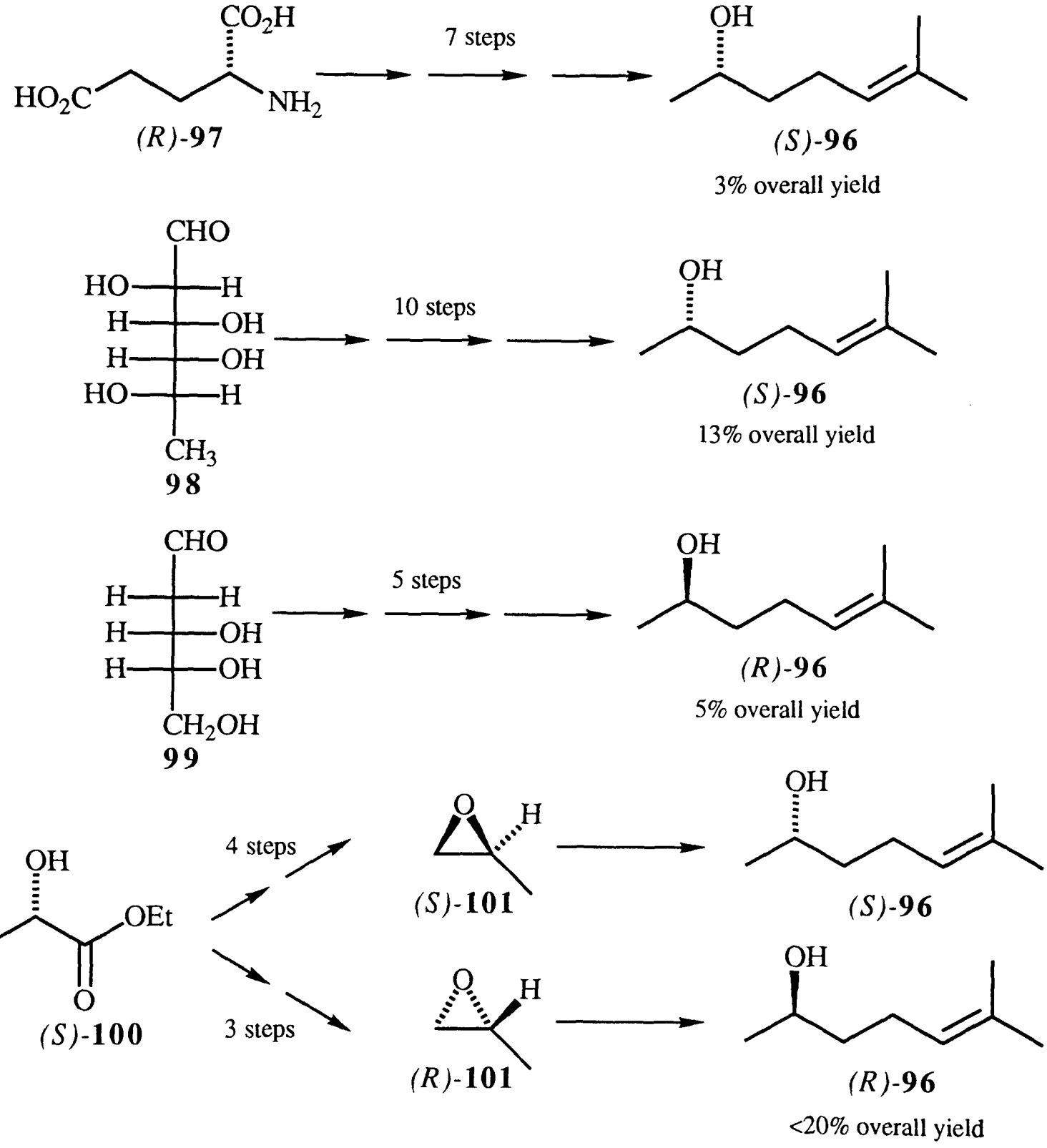
5.2.1 Chemical Methods.

Mori *et al.* made use of *(S)* and *(R)*-glutamic acid (**97**) to prepare both *(R)* and *(S)*-sulcatol (**96**) respectively in 7 steps with an overall yield of 3% (**Scheme 50**).[73]

Carbohydrate starting materials were used to prepare homochiral sulcatol (**96**) by Slessor *et al.* (L)-Fucose (**98**) was converted in 10 steps to *(S)*-sulcatol (**96**) in 13% overall yield. 2-Deoxy-(D)-ribose (**99**) was converted in 5 steps to *(R)*-sulcatol (**96**) in 5% overall yield (**Scheme 50**).[74]

(S)-Ethyl lactate (**100**) was used as starting material by Slessor *et al.*, who also prepared *(R)* and *(S)*-sulcatol (**96**) from *(R)* and *(S)*-propylene oxide (**101**) respectively with an overall yield of less than 20% (**Scheme 50**).[75]

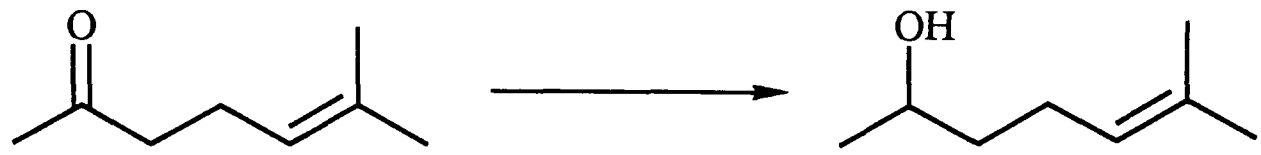
Scheme 50 : Preparation of sulcatol *via* chemical methods.



5.2.2 Enzymic Methods.

Biocatalytic reduction of prochiral 6-methylhept-5-en-2-one (**102**) to give sulcatol (**96**) has been performed using a number of different enzymes as shown in **Scheme 51**.

Scheme 51 : Preparation of sulcatol *via* enzymic reduction.



102 *(R)* or *(S)*-**96**

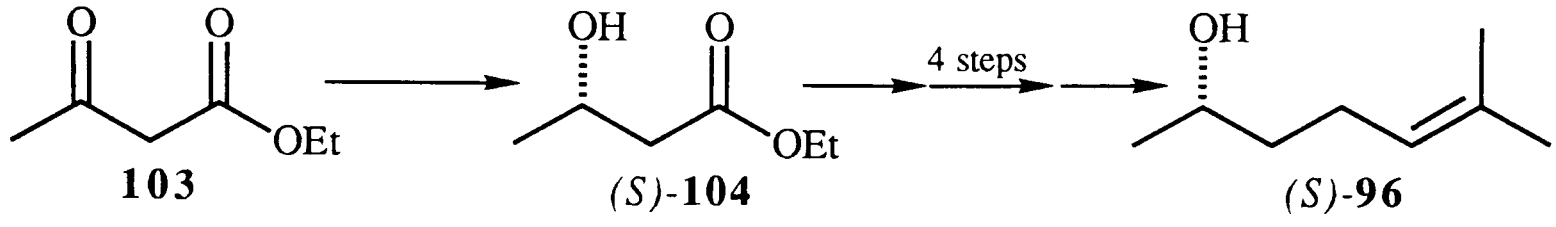
Entry	Enzyme	Product	% yield	% ee	ref.
1	*Lactobacillus kefir.*	*R*	58	>99	76
2	*Pseudomonas* sp. alcohol dehydrogenase.	*R*	51	97	77
3	*Thermoanaerobium brockii.*	*S*	<50[a]	99	78
4	*Thermoanaerobium brockii.*	*S*	52	>99	79
5	*T. brockii* (growing).	*S*	100[b]	>99	79
6	*Clostridium tyrobutyricum.*[c]	*S*	100[b]	88	79
7	*Clostridium tyrobutyricum.*[d]	*R*	53	80	79
8	*Aspergillus niger.*	*R*	64	96	79
9	*Geotrichum candidum.*	*R*	50	92	79
10	Baker's yeast.[e]	*S*	70	94	79
11	Baker's yeast.[e]	no reaction			80
12[f]	Baker's yeast.[e]	*S*	49[g]	85-87	80
13[h]	Baker's yeast.[e]	*S*	19[g]	99	81

[a] Yield unreported, reaction stopped at ~50% conversion. [b] Crude yield. [c] From crotonic acid. [d] From glucose. [e] *Saccharomyces cerevisiae.* [f] Reduction of ethyl acetoacetate followed by conversion to sulcatol. [g] Overall yield. [h] Reduction of 4-nitro-2-butanoate followed by conversion to sulcatol.

Without exception all the reductions described in **Scheme 51** have shortcomings of one form or another. Apart from baker's yeast none of the enzymes mentioned are readily available. Many of the enzymes (entries 1 to 9) require the use of specialist equipment and techniques.[79] Some also require expensive cofactors (entries 1 to 5).

Baker's yeast reduction of 6-methylhept-5-en-2-one (**102**) has been reported twice (entries 10 and 11) with greatly differing results. Veschambre *et al.* obtained *(S)*-sulcatol (**96**) in 70% yield and with an enantiomeric excess of 94%,[79] whereas Mori *et al.* observed no reaction whatsoever.[80] Mori *et al.* did however use baker's yeast to reduce ethyl acetoacetate (**103**) to *(S)*-ethyl 3-hydroxy butyrate (**104**), this was then converted to *(S)*-sulcatol (**96**) with an overall yield of 49% and an enantiomeric excess of 85 - 87% (**Scheme 52**).[80]

Scheme 52 : Preparation of *(S)*-sulcatol (**96**) *via* reduction of ethyl acetoacetate.

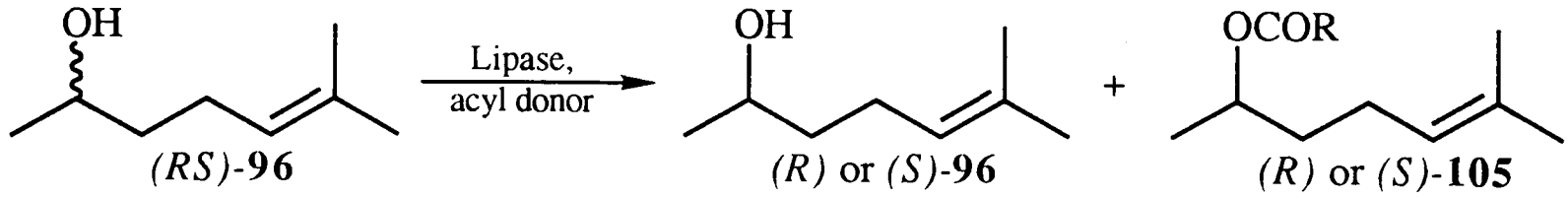


103 *(S)*-**104** *(S)*-**96**

85 - 87% ee, 49% overall yield.

Enzymic kinetic resolution of racemic sulcatol (**96**) has also been used to prepare homochiral sulcatol (**96**) as shown in **Scheme 53**. High enantiomeric excesses can be obtained but as with all simple kinetic resolutions, the maximum yield is limited to 50%.

Scheme 53 : Lipase mediated kinetic resolution of racemic sulcatol (**96**).



(RS)-**96** *(R)* or *(S)*-**96** *(R)* or *(S)*-**105**

Enzyme	Acyl donor	Solvent	Recovered sulcatol (**96**)	E	ref.
PPL	trifluoroethyl laurate	Et_2O	*S*	24	82
dehydrated PPL	trifluoroethyl laurate	Et_2O	*S*	100	82
PPL	trichloroethyl butyrate	Et_2O	*S*	16-23[a]	79
CCL	tributyrin	biphasic system	*R*	39	83

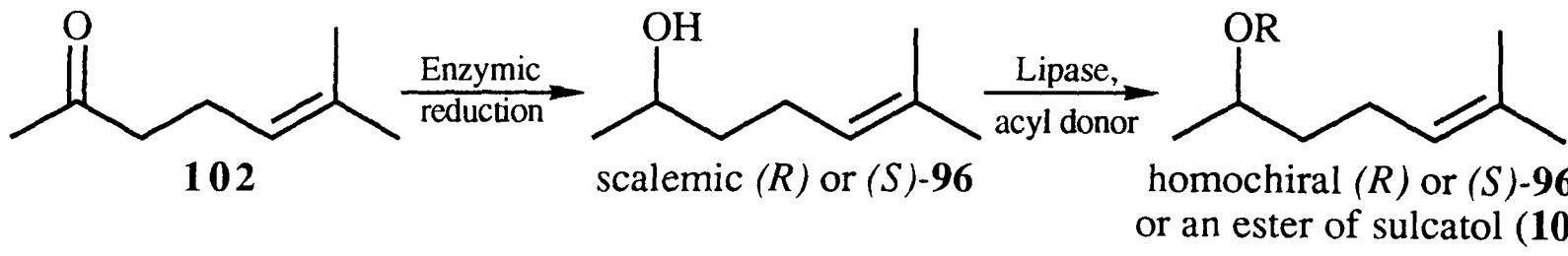
[a] Calculated from the reported conversion and enantiomeric excesses using the standard formulae.[7a]

In addition to the examples shown in **Scheme 53**, Paquette *et al.* obtained homochiral *(S)*-sulcatol (**96**) *via* the lipase P30 mediated hydrolysis of *(RS)*-6-chloroacetoxy-2-methylhept-2-ene. This kinetic resolution was reported to proceed with a stereoselectivity factor of approximately 49.[84]

5.3 Proposed Combination of Asymmetric Synthesis and Kinetic Resolution for the Preparation of *(S)*-Sulcatol (96).

From the enzymic reactions reported it is apparent that a similar strategy to that employed for the preparation of homochiral propan-1,3-diol derivatives (Chapter 4) could be used for the preparation of homochiral sulcatol (**96**). In this case, the prochiral ketone 6-methylhept-5-en-2-one (**102**) is reduced to form optically active sulcatol (**96**). Lipase mediated kinetic resolution of the scalemic sulcatol (**96**) obtained would then enable formation of sulcatol (**96**) [or, depending on the stereochemical preference of the lipase used in the kinetic resolution, an ester of sulcatol (**105**)] with enhanced enantiomeric excess (**Scheme 54**).

Scheme 54 : Proposed strategy for the preparation of homochiral sulcatol *via* two enantioselective reactions.



5.3.1 Exploratory Reactions.

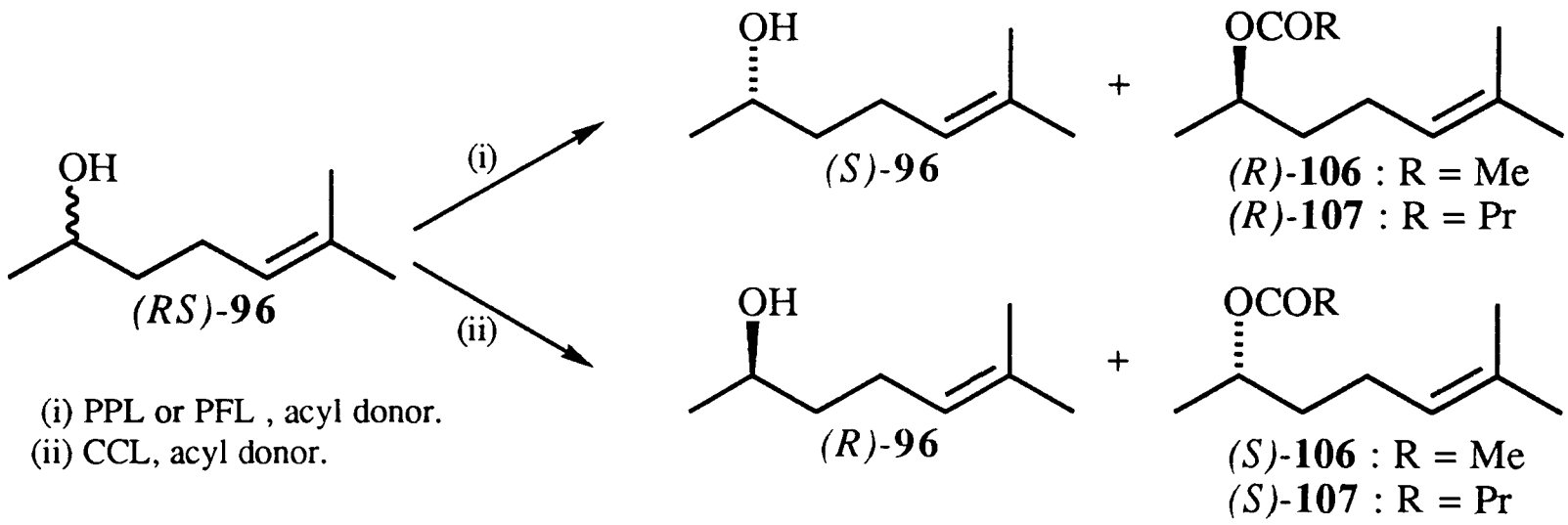
Baker's yeast reduction of 6-methylhept-5-en-2-one (**102**) was performed and contrary to both Veschambre[79] and Mori[80] led to formation of *(S)*-sulcatol (**96**) with an enantiomeric excess of 85% in 66% yield (77% with respect to recovered starting material).

Kinetic resolution of racemic sulcatol (**96**) was performed using a number of lipases to establish which lipase would be most suitable for the second step of the proposed strategy (**Scheme 55**).

PPL and CCL were found to catalyse the kinetic resolution with much lower stereoselectivity factors than those reported in the literature.[79,82,83]

Enantiomeric excesses of sulcatol (**96**) were measured by conversion to Mosher's esters[46] followed by ^1H NMR spectroscopy, enantiomeric excesses of esters of sulcatol (**106** and **107**) were measured by first hydrolysing the ester and then treating in the same way.

Scheme 55 : Lipase mediated kinetic resolution of racemic sulcatol.



(i) PPL or PFL , acyl donor.
(ii) CCL, acyl donor.

Enzyme[a]	Acyl donor	Solvent	Recovered sulcatol (**96**)	E[b]
PPL	vinyl acetate	Et_2O	*S*	3.4
PFL	vinyl acetate	CH_2Cl_2	*S*	4.1
CCL	vinyl acetate	CH_2Cl_2	*R*	3.3
PPL	trichloroethyl butyrate	Et_2O	*S*	4.2
PFL	trichloroethyl butyrate	CH_2Cl_2	*S*	4.6
CCL	trichloroethyl butyrate	CH_2Cl_2	*R*	6.0

[a] *Aspergillus niger* lipase, *mucor javanicus* lipase and *rhizopus arrhizus* lipase were also screened, however no reaction was observed using either vinyl acetate or trifluoroethyl butyrate as acyl donor in dichloromethane. [b] Calculated according to the standard formulae.[7a]

From the experiments performed (**Scheme 55**), with each lipase use of trichloroethylbutyrate as acyl donor gave rise to a higher stereoselectivity factor than when vinyl acetate was used.

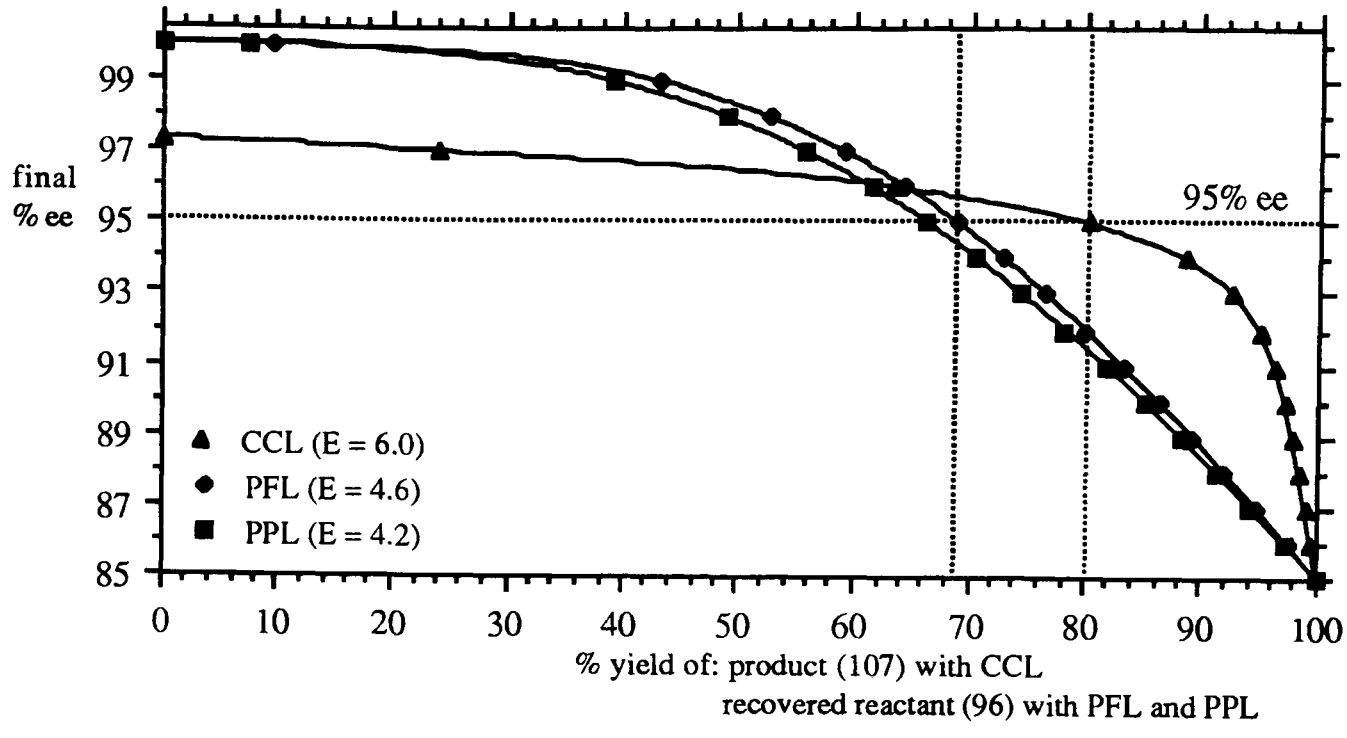
After the completion of this work Carrea *et al.* reported the kinetic resolution of racemic sulcatol (**96**) in a number of different solvents using PPL and lipase PS. Their results indicate that more selective systems are available for the kinetic resolution of sulcatol (**96**). In particular, the use of PPL in benzene with trifluroethyl butyrate as acyl donor is reported to proceed with a stereoselectivity factor of 62.[85]

5.4 Application of the Proposed Strategy.

The first step in the process was the baker's yeast mediated reduction of 6-methylhept-5-en-2-one (**102**) to give *(S)*-sulcatol (**96**) with an enantiomeric excess of 85%. From the experiments performed in **Scheme 55** there was a choice of which lipase to use in the acylation step. With CCL, the faster reacting enantiomer of sulcatol (**96**) is the *S* enantiomer. Since sulcatol (**96**) obtained from baker's yeast reduction of **102** is enriched in the *S* enantiomer, use of CCL in the acylation step would lead to formation of product (**107**) with enhanced enantiomeric excess (see Section 1.4.5.1). With PFL and PPL, the faster reacting enantiomer of sulcatol (**96**) is the *R* enantiomer. Therefore if PFL or PPL were used in the acylation step it would lead to recovered reactant (**96**) (rather than the product) with enhanced enantiomeric excess (see Section 1.4.5.2).

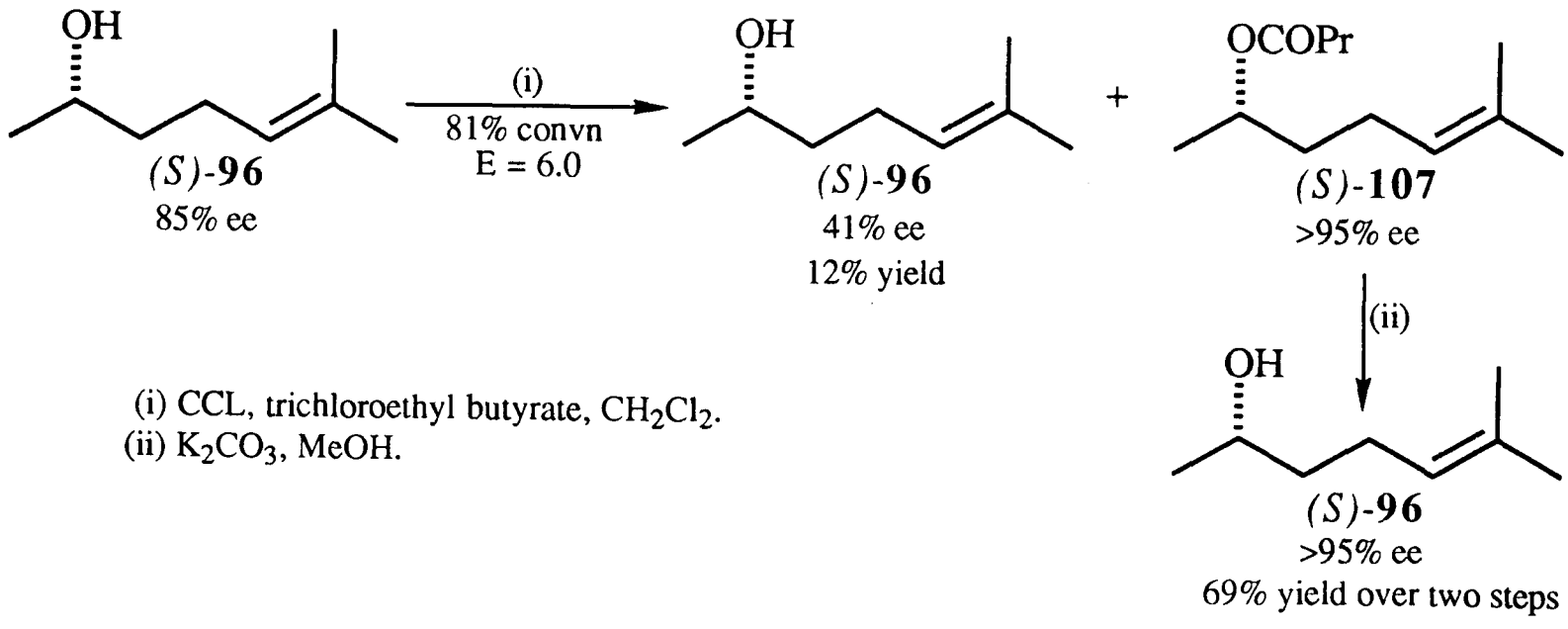
Use of the computer model (Appendix 1) enabled a plot of % yield against % enantiomeric excess (of product [**107**] or recovered reactant [**96**], depending on which lipase was used in the kinetic resolution) to be made (**Figure 20**). This indicated that for a final enantiomeric excess of 95%, maximum yield would be obtained using CCL in the acylation step (rather than PFL or PPL) and by allowing the reaction to run to 80% conversion. If PFL was used in the acylation step, recovered reactant (**96**) with 95% enantiomeric excess would be obtained after 31% conversion (corresponding to 69% yield of recovered reactant).

Figure 20 : Plot of % yield versus % enantiomeric excess of product (**107**) (in the case of CCL) or % enantiomeric excess of recovered reactant (**96**) (in the case of PFL and PPL) obtainable by acylation of *(S)*-sulcatol (**96**) (85% ee) with various lipases.



Therefore, to complete the two step process, CCL mediated acylation of *(S)*-sulcatol (**96**) (85% ee) was performed as shown in **Scheme 56**. After 81% conversion, recovered starting material (**96**) was obtained in 12% yield and with an enantiomeric excess of 41% (model predicted 43%), and the required product *(S)*-(**107**) was obtained in 73% yield. Simple hydrolysis of **107** yielded *(S)*-sulcatol (**96**) in 94% yield and with >95% enantiomeric excess.

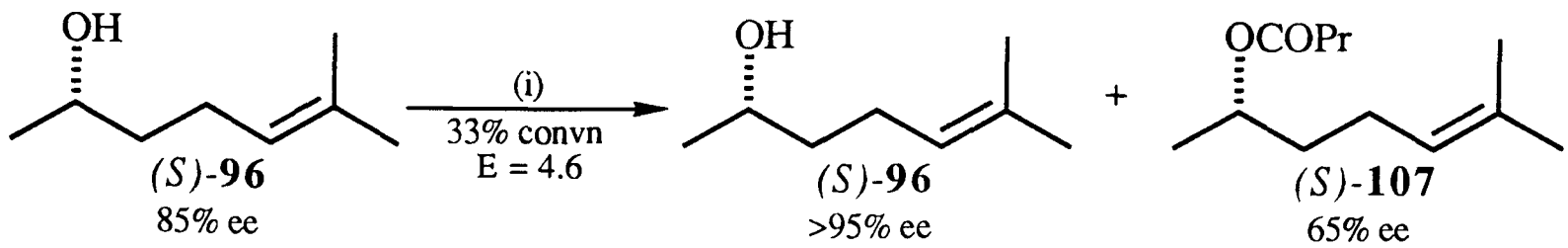
Scheme 56 : CCL mediated acylation of *(S)*-sulcatol (**96**) (85% ee).



(i) CCL, trichloroethyl butyrate, CH_2Cl_2.
(ii) K_2CO_3, MeOH.

PFL mediated acylation of *(S)*-sulcatol (**96**) (85% ee) was also performed as shown in **Scheme 57** and yielded recovered starting material *(S)*-sulcatol (**96**) in 59% yield with >95% enantiomeric excess and product (**107**) in 24% yield with 65% enantiomeric excess (model predicted 64%).

Scheme 57 : PFL mediated acylation of *(S)*-sulcatol (**96**) (85% ee).



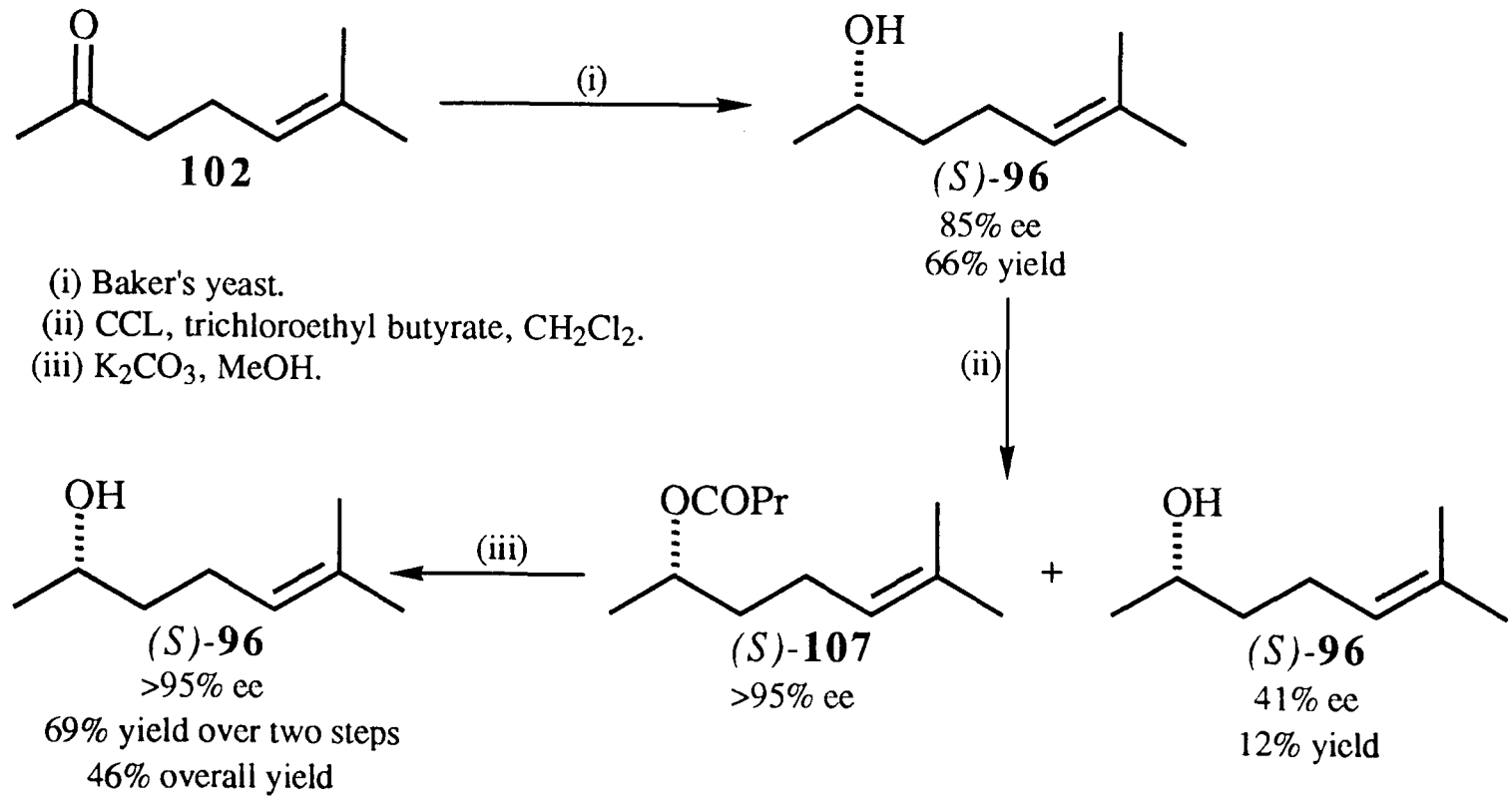
(i) PFL, trichloroethyl butyrate, CH_2Cl_2.

5.5 Summary and Conclusion.

(S)-Sulcatol (**96**) has been prepared by a technique involving enzymic reduction followed by kinetic resolution.

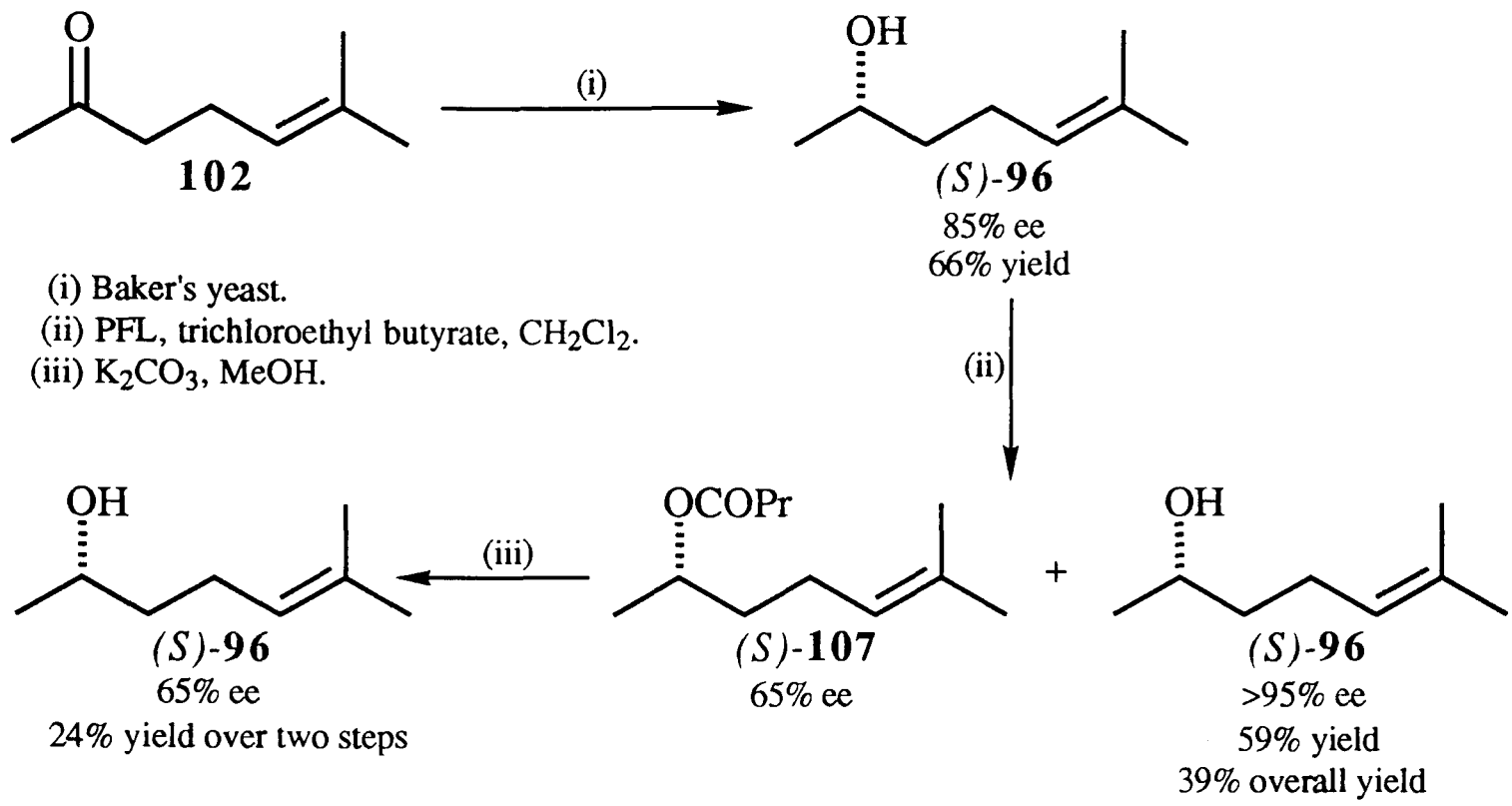
Overall yield of *(S)*-sulcatol (**96**) (>95% ee), starting from 6-methylhept-5-en-2-one (**102**), was 46% when CCL was used in the second step (**Scheme 58**) and 39% when PFL was used in the second step (**Scheme 59**.)

Scheme 58 : Preparation of *(S)*-sulcatol (**96**) using CCL in the second step.



(i) Baker's yeast.
(ii) CCL, trichloroethyl butyrate, CH_2Cl_2.
(iii) K_2CO_3, MeOH.

Scheme 59 : Preparation of *(S)*-sulcatol (**96**) using PFL in the second step.



When compared with conventional enzymic methods for the preparation of sulcatol (**96**), the procedure used here is not as efficient as the best enzymic reductions (**Scheme 51**) or the best enzymic kinetic resolutions (**Scheme 53**). However, the procedure described uses inexpensive enzymes, requires no specialist equipment and as such serves to demonstrate the proposed strategy.

There is no reason why the strategy described above cannot be applied generally for the preparation of suitable alcohols in homochiral form. A number of recent publications[86] describe enzymic kinetic resolutions of a racemic alcohol and also describe enzymic reduction of the ketone precursor to the same alcohol. In each case, combination of the two processes in a similar manner to that described above should enable enhanced yield and/or enhanced enantiomeric excesses to be obtained.

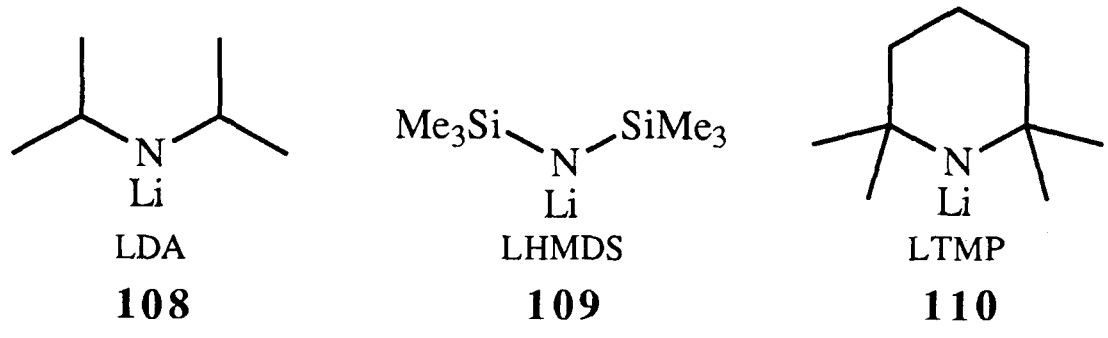
Chapter 6

Investigation of the Structure of lithium(α-methylbenzyl)benzyl amide.

6.1 Uses of Homochiral Lithium Amides.

Lithium amides such as lithium diisopropylamide (LDA) (**108**), lithium hexamethyldisilazide (LHMDS) (**109**) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) (**110**) (**Figure 21**) have many applications in modern organic chemistry principally as non-nucleophilic bases. Due to the ever increasing interest in the preparation of homochiral material it comes as no surprise that the use of homochiral lithium amides has been the subject of much recent investigation.[87]

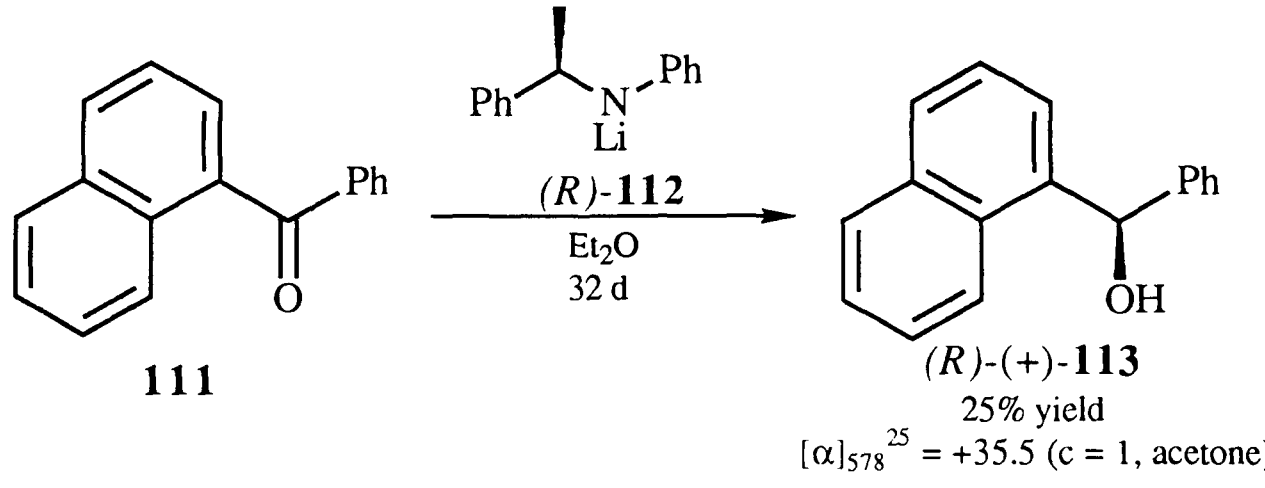
Figure 21 : Commonly used lithium amides.



As a consequence of the ready availability of many homochiral amines (often in both enantiomeric forms), and their simple conversion to lithium amides, homochiral lithium amides are cheap, convenient sources of chirality.

In 1969 Wittig *et al.* published the first reported use of a homochiral lithium amide in which phenyl(α-naphthyl)ketone (**111**) was enantioselectively reduced using lithium(α-methylbenzyl)phenyl amide (**112**) to form the secondary alcohol (**113**) in 25% yield after stirring for 32 d (not 32 h as reported in reference 87) in diethyl ether (**Scheme 60**). The product obtained (**113**) had a specific rotation of $[\alpha]_{578}^{25} = +35.5$ (c = 1, acetone).[88]

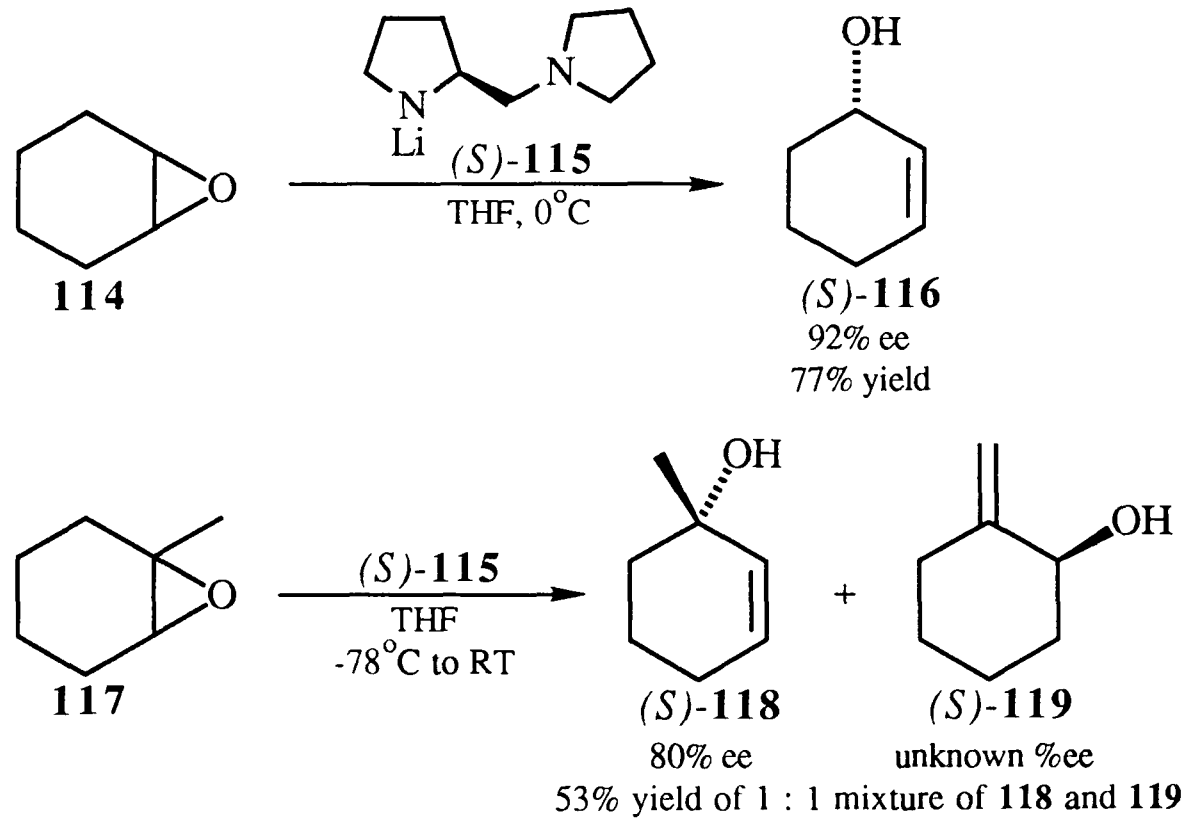
Scheme 60 : Enantioselective reduction using a homochiral lithium amide.



Whitesell *et al.* first demonstrated that deprotonation of epoxides using homochiral lithium amides can lead to the formation of optically active allylic alcohols.[89] This technique was used by Asami *et al.* in the preparation of *(S)*-2-cyclohexen-1-ol (**116**) by the treatment of cyclohexene oxide (**114**) with the proline derived homochiral lithium amide (**115**). The product (**116**) was obtained in 77% yield and with an enantiomeric excess of 92% (**Scheme 61**).[90]

Mori *et al.* prepared one of the aggregation pheromones of the Douglas-fir beetle by the homochiral lithium amide mediated rearrangement of racemic 1-methylcyclohexene oxide (**117**) with the same homochiral lithium amide (**115**) as described above. In this case the required product *(S)*-1-methyl-2-cyclohexen-1-ol (**118**) and the exocyclic allylic alcohol (**119**) were obtained as a 1 : 1 mixture in 53% yield. Separation of **118** and **119** by preparative GLC enabled the enantiomeric excess of **118** to be estimated at 80% (**Scheme 61**).[91]

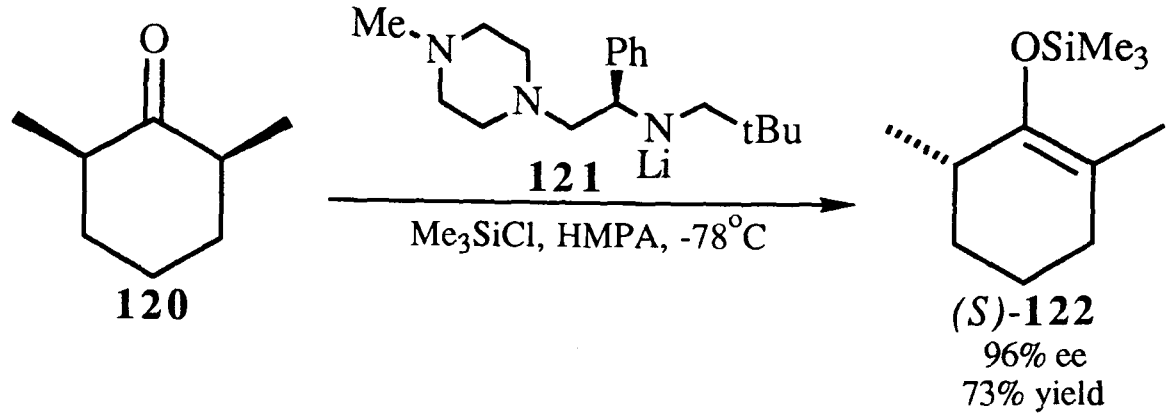
Scheme 61 : Homochiral lithium amide mediated epoxide rearrangement.



Deprotonation of the cyclic prochiral ketone *cis*-2,6-dimethylcyclohexanone (**120**) with the homochiral lithium amide (**121**), in the presence of one equivalent of hexamethyl-phosphoramide (HMPA), followed by trapping with trimethylsilyl chloride, led to

formation of the silylated enol *(S)*-**122** in 73% yield and with an enantiomeric excess of 96% as shown in **Scheme 62**.[92]

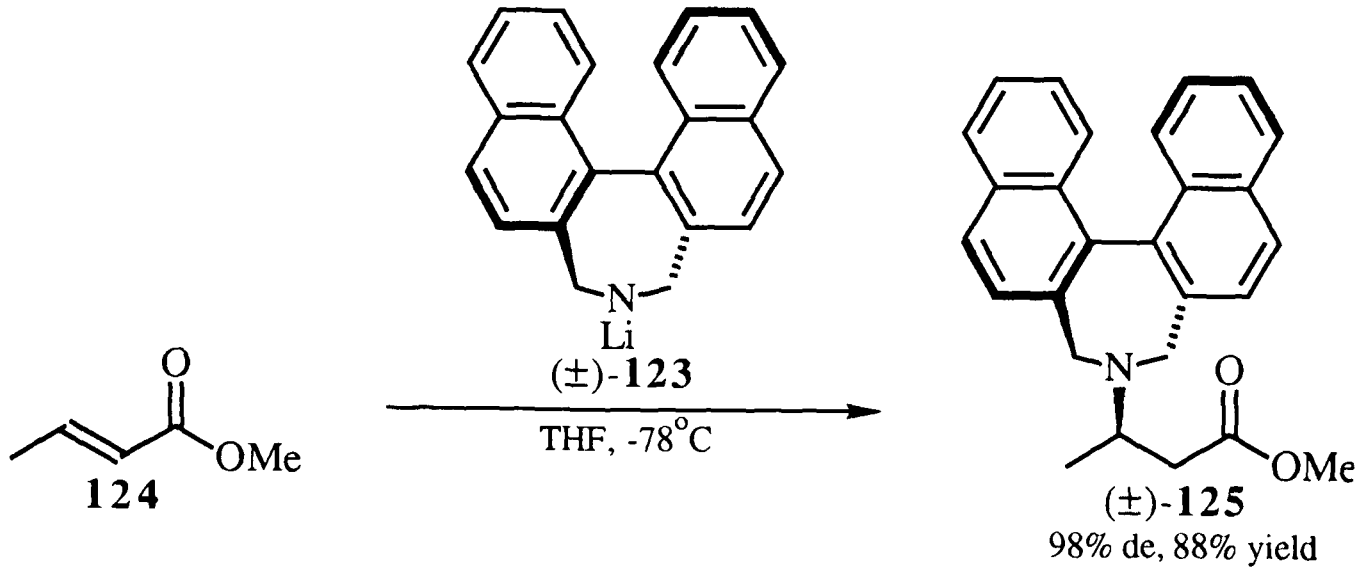
Scheme 62 : Deprotonation of a prochiral cyclic ketone using a homochiral lithium amide.



There are many other examples in the chemical literature in which homochiral lithium amides have been employed. These include enantioselective [2,3]-Wittig ring contractions;[93] enantioselective dehydrohalogenations;[94] and kinetic resolution of imidazolidinones and β-lactams.[95]

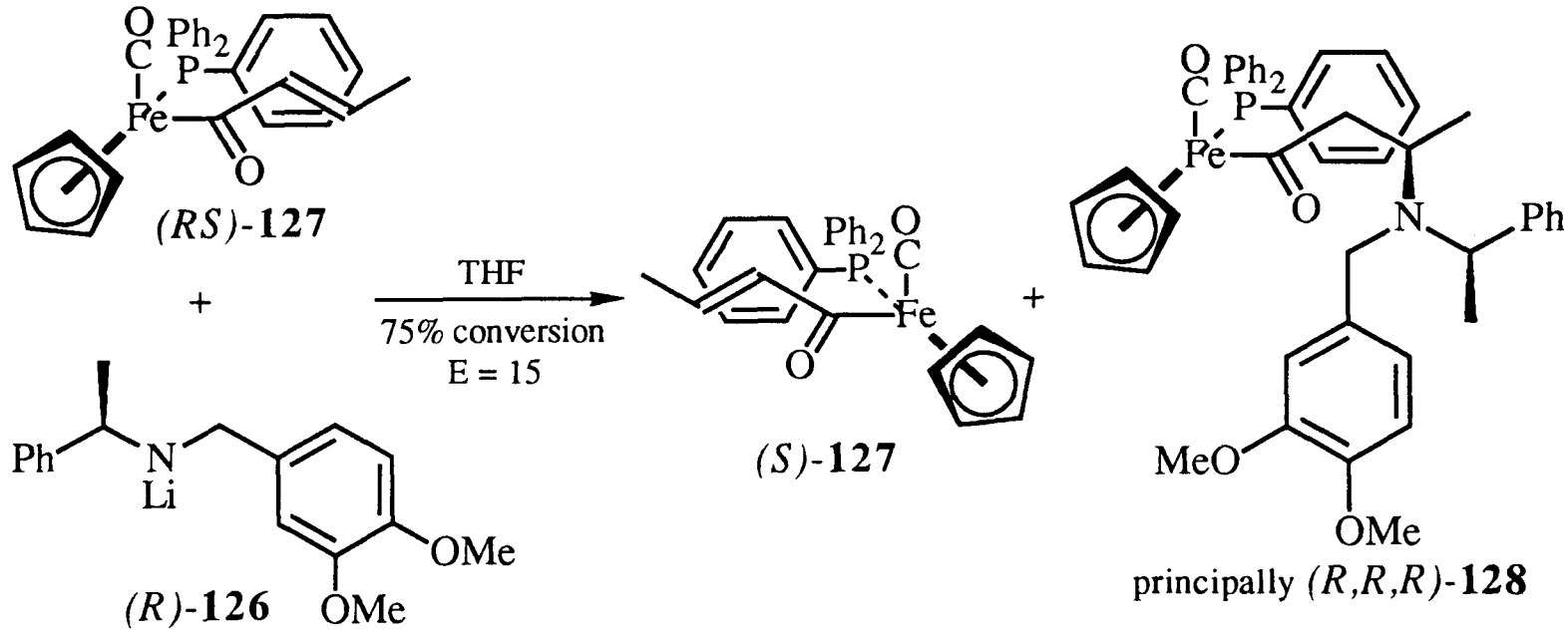
A more recent development is the use of homochiral lithium amides as nucleophiles in Michael addition reactions. This was first demonstrated by Hawkins *et al.* using the binaphthyl derived lithium amide (**123**). Treatment of methyl crotonate (**124**) with 4 equivalents of racemic **123** gave product **125** in 88% yield and with a diastereomeric excess of 98% (**Scheme 63**).[96] Hydrogenolysis of Michael adducts so formed (with homochiral **123**) enabled the preparation of β-amino esters with moderate overall yields (32 - 70%) and high enantiomeric excess (95 - 99%).[97]

Scheme 63 : Lithium amide Michael addition to methyl crotonate.



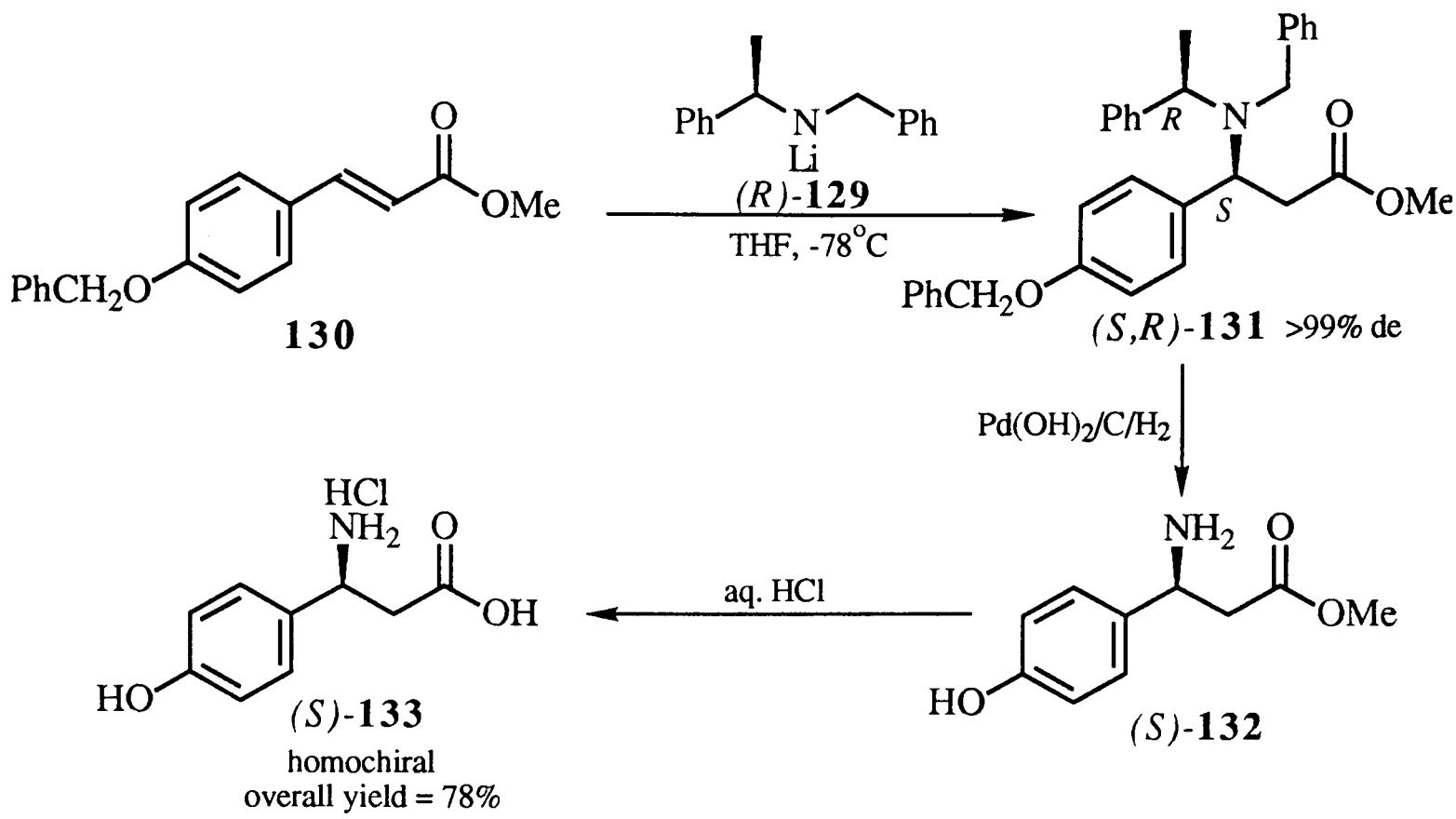
Investigation of homochiral lithium amides in our group began with the Michael addition of lithium N-(3,4-dimethoxybenzyl)-α-methylbenzyl amide (**126**) to the iron crotonyl complex (**127**). When racemic **126** and racemic **127** were used the diastereomeric ratio of product (**128**) obtained was 94 : 3 : 3 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*]. This indicated a ratio of specific rate constants of 16 : 1 for reaction of the matched pair [*(R)*-amide (**126**) + *(R)*-iron complex (**127**) {or *(S)*-**126** + *(S)*-**127**}] and the mismatched pair [*(R)*-amide (**126**) + *(S)*-iron complex (**127**) {or *(S)*-**126** + *(R)*-**127**}]. Therefore reaction of racemic iron complex (**127**) and *(R)*-lithium amide (**126**) resulted in kinetic resolution of the iron complex (**127**) (which proceeded with a stereoselectivity factor (E) of 15) (**Scheme 64**).[98]

Scheme 64 : Kinetic resolution of *(RS)*-iron crotonyl complex (**127**) with lithium N-(3,4-dimethoxybenzyl)[*(R)*-α-methylbenzyl] amide (**126**).



Davies *et al.* have also performed Michael additions with a number of homochiral lithium amides to a wide range of α,β-unsaturated esters[99] and amides.[100] For example, Michael addition of lithium[*(R)*-α-methylbenzyl]benzyl amide (**129**) to methyl-*p*-benzyloxycinnamate (**130**) proceeded in 78% yield to give the *(S,R)*-adduct (**131**) with a diastereomeric excess of >99%. Hydrogenolysis of *(S,R)*-**131** yielded the *(S)*-β-amino ester (**132**) in quantitative yield. Subsequent acidic hydrolysis gave the hydrochloride salt of homochiral *(S)*-β-tyrosine (**133**) also in quantitative yield (**Scheme 65**).[99]

Scheme 65 : Preparation of*(S)*-β-tyrosine.HCl (**133**) using a homochiral lithium amide.



6.2 The Structure of Lithium Amides.

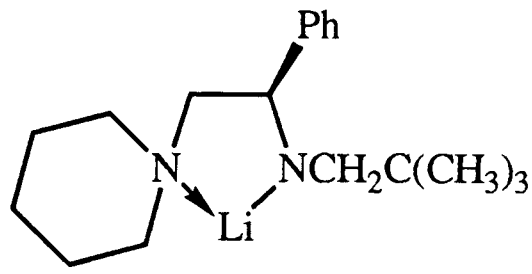
In order to understand how homochiral lithium amides are able to react as selectively as they do it is essential that the structures of the homochiral lithium amides involved are known. Consequently, there is a great deal of interest in the determination of the structures of lithium amides.[101]

Many different methods have been employed for the determination of lithium amide structures. These include X-ray crystallography;[102] multinuclear NMR spectroscopy;[103] molecular mass determination using colligative properties[104] and molecular modelling calculations.[105]

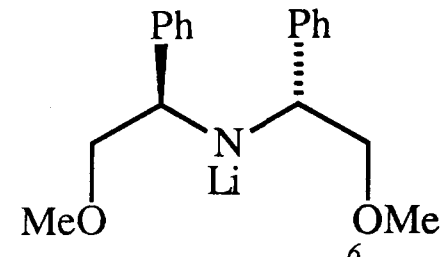
From the various studies performed it has been shown that lithium amides are capable of aggregating to form dimers,[106] trimers,[107] tetramers[108] or even higher aggregates,[109] although some lithium amides do exist as monomers (**Figure 22**).[110] In addition to molecular structure, the degree of aggregation of lithium amides depends greatly on solvent, temperature and concentration. With chiral lithium amides (in racemic form) there is the added complication that aggregation can lead to the formation of diastereomeric

species. As well as their complexity, structure elucidation of lithium amides is also hindered by their sensitivity to air and moisture.

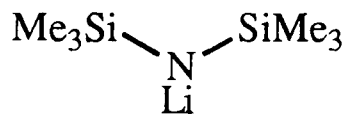
Figure 22 : The diversity of lithium amide structures.



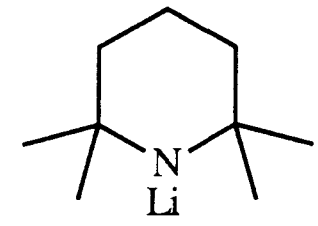
monomer in THF
(R)-**134**[110]



dimer in benzene-d^6
(R,R)-**135**[106]



crystallised as a trimer from benzene
109[107]



crystallised as a tetramer from hexane-pentane
110[108]

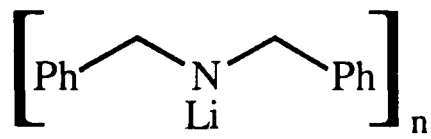
6.3 Structure Investigation of lithium(α-methylbenzyl)benzyl amide (129).

Previous work in our group has made use of lithium(α-methylbenzyl)benzyl amide (**129**) and found it capable of performing highly selective addition reactions to a number of Michael acceptors (for example, see **Schemes 64** and **65**).[98,99,100] In order to aid the understanding of these reactions it was desirable to investigate the structure of this lithium amide in THF solution.

6.3.1 Structures of Lithium Amides similar to 129.

The chemical literature reports structures for a number of similar lithium amides. In particular Snaith *et al.* found that lithium dibenzylamide (**136**) crystallises from a toluene-hexane mixture as a cyclic trimer (**137**) containing a planar six-membered $(NLi)_3$ ring. From diethyl ether-hexane or HMPA-hexane, the same lithium amide (**136**) was found to crystallise as a cyclic dimer (**138** and **139** respectively) containing a planar four-membered $(NLi)_2$ ring (**Figure 23**).[111]

Figure 23 : Structures of lithium dibenzylamide (**136**).



136

$[(PhCH_2)_2NLi]_3$

crystallised from toluene-hexane

137

$[(PhCH_2)_2NLi.OEt_2]_2$

crystallised from diethyl ether-hexane

138

$[(PhCH_2)_2NLi.O{=}P(NMe_2)_3]_2$

crystallised from HMPA-hexane

139

Snaith *et al.* also predicted that since the benzyl groups in **137**, **138**, and **139** do not lie in the same plane as the NLi ring, ring stacking[109b] is not possible. Ring laddering[109b] is also improbable for steric reasons with **137** and because of the presence of solvent molecules in **138** and **139**. Therefore with **136**, the formation of aggregates larger than trimers can be ruled out.[112]

Relative molecular mass measurements of **137** and **138** at different concentrations in benzene have been performed. With **137**, n = 2.87 - 2.72 (where n = the degree of aggregation). This is thought to indicate that a trimeric structure largely persists in solution but that a dimeric and/or monomeric species is also present. In the case of **138**, n = 1.16 - 1.06. This was interpreted as being caused by extensive dissociation of the crystalline dimer to form a monomer, or possibly due to loss of the diethyl ether molecules and formation of an unsolvated dimer which then proceeds to disproportionate to the same trimer/dimer/monomer equilibrium observed for **137**.[113] Snaith *et al.* have also performed ^{7}Li NMR spectroscopic studies of **137** and **138** in benzene. The results obtained agree well with the trimer/dimer/monomer equilibrium mentioned above.[113]

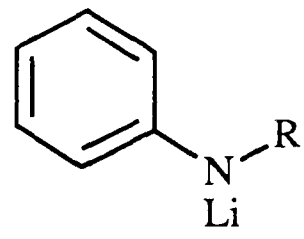
Molecular orbital calculations have suggested that the pink-red coloration of solutions of **137** and **138** can only arise from electronic transitions taking place in uncomplexed monomeric $(PhCH_2)_2NLi$ rather than from transitions in an aggregated structure.[114]

In the reaction of lithium N-(3,4-dimethoxybenzyl)[*(RS)*-α-methylbenzyl] amide (**126**) with *(RS)*-iron crotonyl complex (**127**) it was observed that if 1 equivalent of the

lithium amide (**126**) was used, ~ 50% yield of product (**128**) was obtained. If 0.5 equivalents of **126** were used, the yield of **128** was ~ 25% and with 2 equivalents of **126** a yield of >90% of **128** was obtained. These observations indicated that the reaction proceeded with a 2 : 1 stoicheiometry of lithium amide (**126**) : iron complex (**127**). This was interpreted as being caused by the lithium amide (**126**) reacting as a dimer. Furthermore, due to the consistency of the result obtained when kinetic resolution of *(RS)*-iron complex (**127**) with *(R)*-lithium amide (**126**) (**Scheme 64**) was performed and the result obtained in the reaction of *(RS)*-iron complex (**127**) with *(RS)*-lithium amide (**126**), it was postulated that the dimers of the lithium amide (**126**) must be homochiral [*(RS,RS)*] rather than heterochiral [*(RS,SR)*].[98]

To the best of our knowledge only monomeric and dimeric structures have been reported for the structure of lithium amides in THF. For example, Jackman *et al.* used ^{13}C NMR spectroscopy and colligative property measurements to determine the structures of the lithium amides shown in **Figure 24**.[115] With the N-alkyl anilides (**140**), the structures at the given temperatures change from monomer-dimer mixtures to exclusively monomers as the steric bulk of the alkyl group increases.

Figure 24 : Structure of lithium amides of N-alkyl anilides (**140**) in THF.



140

R = CH_3, -60°C : monomer - dimer
R = Bu, -100°C : monomer - dimer
R = iPr, -80°C : exclusively monomer
R = tBu, -110°C : exclusively monomer

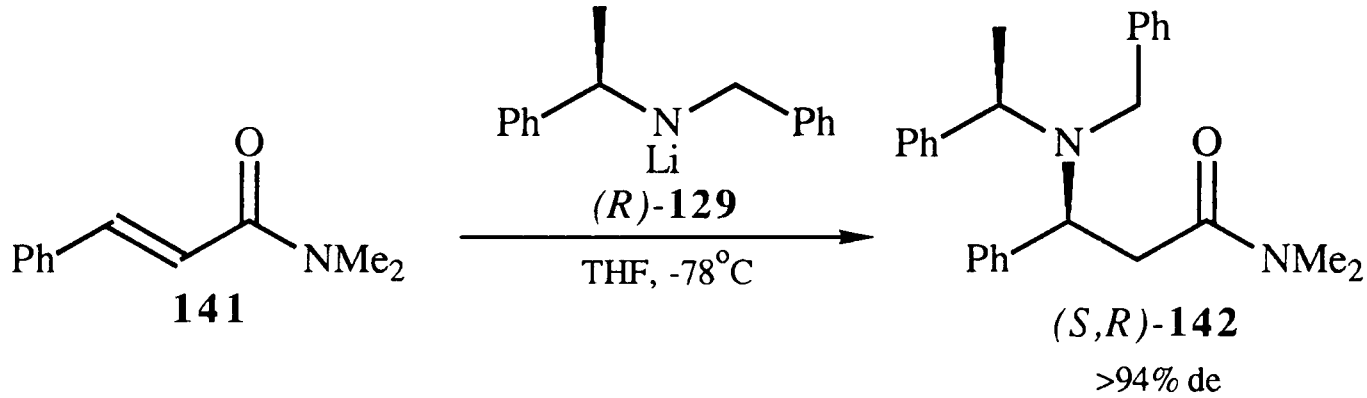
Similarly, lithium hexamethyldisilazide (**109**) is reported to exist as a monomer-dimer mixture in THF at -60°C.[116] Seebach *et al.* observed that lithium diisopropylamide (LDA) (**108**) exists as a monomer-dimer mixture in THF at -108°C,[117] although later work by Collum *et al.* only saw evidence for a dimeric LDA structure under the same conditions.[118]

In view of the above observations, it was thought fair to assume that the structure of **129** in THF at -78°C was likely to be monomeric or dimeric rather than a higher order aggregate.

6.3.2 Experiments performed with N,N-dimethyl cinnamide (141).

It was known that the reaction between lithium[*(R)*-α-methylbenzyl]benzyl amide (**129**) and N,N-dimethyl cinnamide (**141**) proceeded to give the *(S,R)*-Michael adduct (**142**) in high yield and with a diastereomeric excess >94% (**Scheme 66**).[119] Since this reaction proceeded so cleanly to give essentially only one product diastereomer, it was thought that it would be an ideal reaction to study in more detail. It was hoped that from this, information concerning the structure of **129** could be obtained.

Scheme 66 : Reaction of lithium[*(R)*-α-methylbenzyl]benzyl amide (**129**) with N,N-dimethyl cinnamide (**141**)



As mentioned previously, the 2 : 1 stoicheiometry observed in the reaction of *(RS)*-lithium N-(3,4-dimethoxybenzyl)-α-methylbenzyl amide (**126**) with *(RS)*-iron crotonyl complex (**127**) (**Scheme 64**) was interpreted as being caused by the lithium amide (**126**) reacting as a dimer. Therefore experiments were performed to establish the stoicheiometry of the reaction between lithium-(α-methylbenzyl)benzyl amide (**129**) and N,N-dimethyl cinnamide (**141**). Two series of reactions were performed [firstly with *(R)*-**129** and then with *(RS)*-**129**] using varying amounts of **129**. ^{1}H NMR spectroscopy of the crude products (from each reaction) enabled measurement of the extent of conversion of the starting material (**141**) to the product (**142**). These values (shown in **Table 6**) were used to calculate the stoicheiometries of the reactions between homochiral **129** and **141**, and

between racemic **129** and **141**. With *(R)*-**129** and **141** a 1 : 1 stoicheiometry was observed. Similarly with *(RS)*-**129** and **141** a 1 : 1 stoicheiometry was observed.

Table 6 : Experiments performed to establish the stoicheiometry of the reaction between lithium(α-methylbenzyl)benzyl amide (**129**) and N,N-dimethyl cinnamide (**141**).

Entry	Equivalents of **129**	Stereochemistry of **129**	% Conversion to product **143**[a]
1	0.5	*R*	49
2	1.0	*R*	>95
3	1.5	*R*	>95
4	0.5	racemic	47
5	1.0	racemic	>95

[a] Calcuated from NMR spectroscopy of the crude product.

These observations at first suggest that both homochiral and racemic lithium amide (**129**) must be reacting in a monomeric form. However the results do not necessarily rule out the possibility of **129** reacting in a dimeric form, since similar results would be expected if, after addition, the unused half of the dimer were able to return to the reaction medium (as a monomer) and reequilibrate to form more reactive dimers.

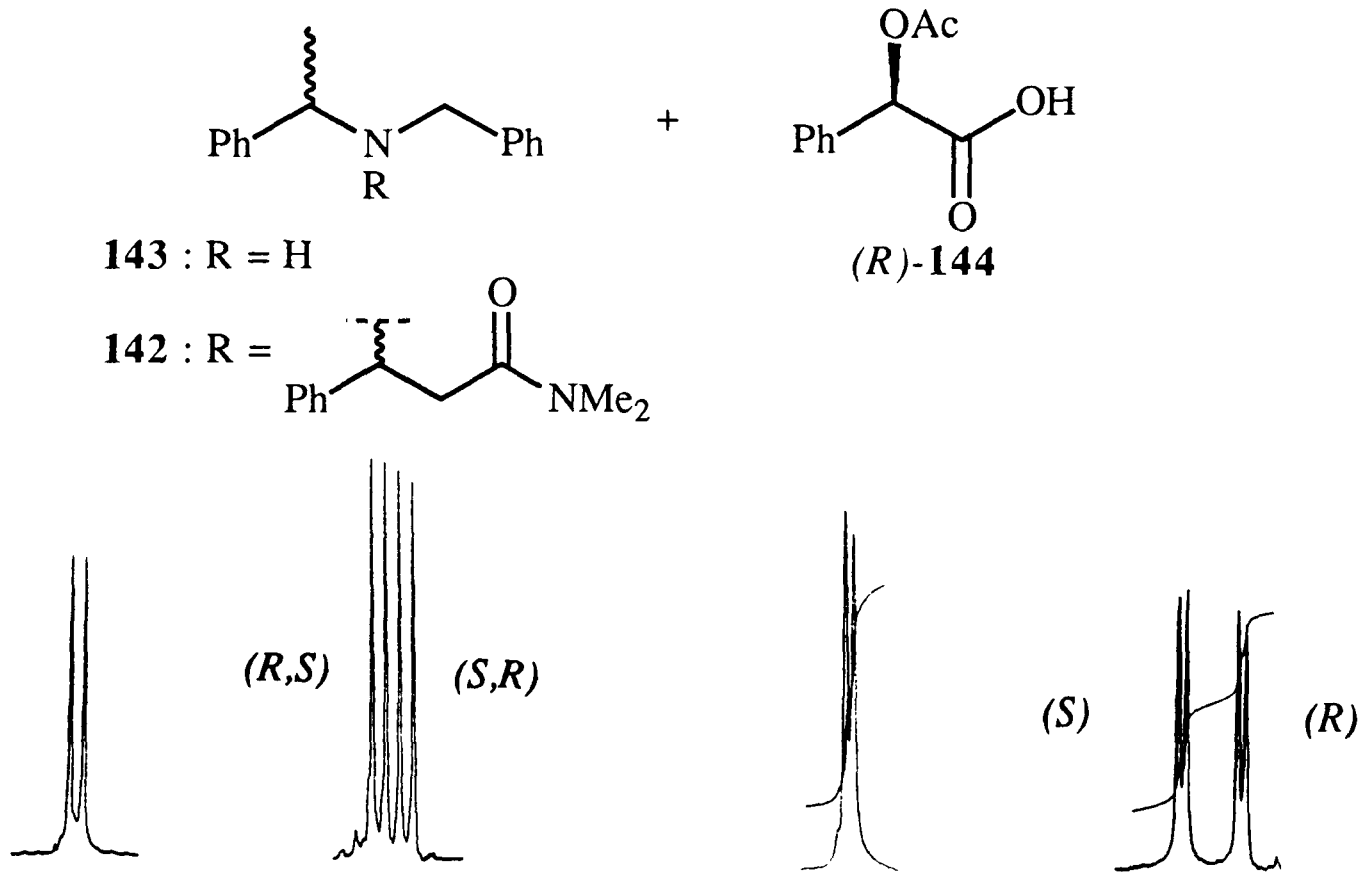
It is often assumed that the enantiomeric excess of a chiral reagent (or chiral auxiliary) and the enantiomeric excess of the product obtained by using such a chiral reagent (or chiral auxiliary) will have a linear relationship. Work by Kagan *et al.* has shown that this is not always the case and that when the relationship is nonlinear, information concerning the reaction mechanism can be obtained. For example, Kagan used this method to demonstrate that in the Sharpless epoxidation,[38] more than one tartrate ligand must be involved in the reactive oxidant species.[120] If a nonlinear effect is observed it is evidence that the chiral reagent (or chiral auxiliary) must be forming aggregates.

In order to investigate further the reaction of lithium(α-methylbenzyl)benzyl amide (**129**) and N,N-dimethyl cinnamide (**141**), experiments were performed to establish whether or not a nonlinear effect existed. If a nonlinear effect was observed, it would be a positive indication that **129** was forming dimers. Thus, reactions were performed using

lithium amide (**129**) with a range of enantiomeric excesses. Measurement of the enantiomeric excesses of the product (**142**) and recovered amine (**143**) (since an excess was used) were performed and the results obtained are shown in **Table 7** and graphically in **Figure 26**.

Before the existence of any nonlinear effect could be investigated, accurate methods for measuring the enantiomeric excesses of the starting amine (**143**) and the Michael adduct (**142**) were required. Parker *et al.* measured the enantiomeric excesses of a number of amines by the addition of one equivalent of *(R)*-O-acetyl mandelic acid (**144**), to form diastereomeric salts, followed by ^1H NMR spectroscopic analysis.[121] This method proved successful with the two amines (**142** and **143**) mentioned above. With **143**, the NMR spectroscopy was performed in $CDCl_3$ at 200 MHz, whereas with **142**, 500 MHz NMR spectroscopy in C_6D_6 was required. In each case enantiomeric excesses were measured by integration of the α-methyl doublets at approximately 1.0 - 1.3 ppm (**Figure 25**). For **142**, the doublet arising from the *S,R* enantiomer appears at higher field. For **143**, the doublet arising from the *R* enantiomer appears at higher field.

Figure 25 : Methods for measuring enantiomeric excesses of **142** and **143**.



homochiral **142** racemic **142**
each + one equivalent of *(R)*-**144**
C_6D_6, 500 MHz.

homochiral **143** racemic **143**
each + one equivalent of *(R)* -**144**
$CDCl_3$, 200 MHz.

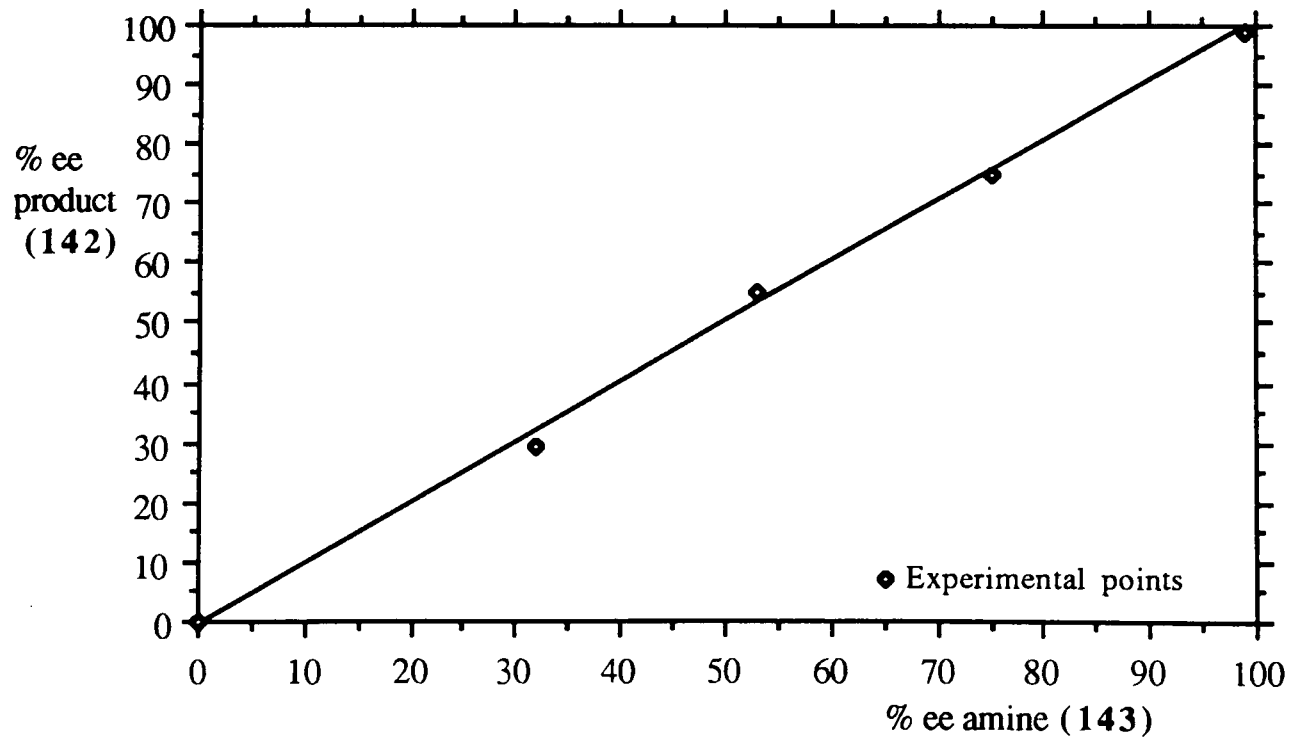
Once a suitable analytical method had been found, the reactions shown in **Table 7** were performed. In each case the diastereomeric excess of the product was identical (>94%).

Table 7 : % Enantiomeric excess of (α-methylbenzyl)benzylamine (**143**) and % enantiomeric excess of product (**142**).

entry[a]	% ee of **143**[b]	% ee of product (**142**)	% ee of recovered **143**[b]
1	0	0	-
2	32	29	30
3	53	55	50
4	75	75	73
5	>97	>97	-
6[c]	52	47	47
7[d]	56	49	58

[a] Performed using 1.6 equivalents of lithium amide **129** unless otherwise stated. [b] Enriched in *(S)*-**143**. [c] Using 10 equivalents of **129**. [d] Performed in toluene.

Figure 26 : Plot of % enantiomeric excess of the chiral reagent (**143**) versus % enantiomeric excess of the product (**142**).



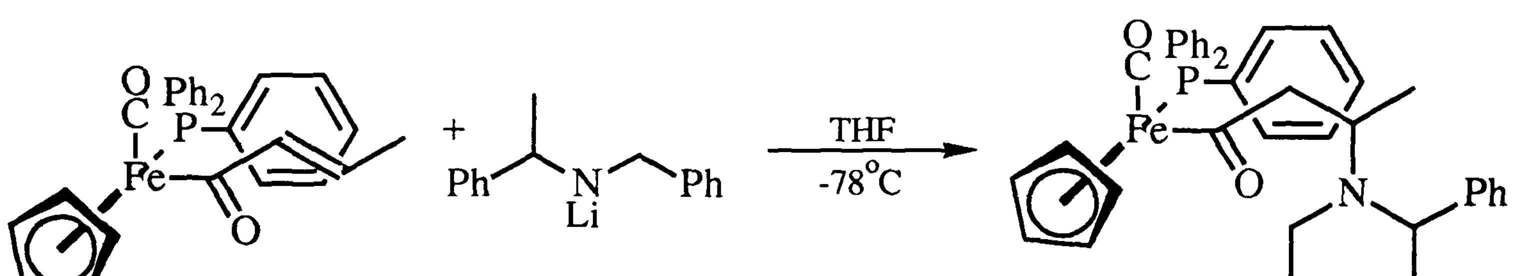
The results obtained indicate that there is no nonlinear effect in the reaction of lithium(α-methylbenzyl)benzyl amide (**129**) and N,N-dimethyl cinnamide (**141**).

Unfortunately, little information can be obtained when no nonlinear effect is observed.[120] All that can be concluded is that either heterochiral dimers (of **129**) do not exist or, if they do exist, they react with the same selectivity and rate as the monomer or homochiral dimer.

6.3.3 Experiments performed with the iron crotonyl complex (127).*

In view of the observation made by Davies *et al.* that the stoicheiometry of the reaction between *(RS)*-lithium N-(3,4-dimethoxybenzyl)-α-methylbenzyl amide (**126**) and the iron crotonyl complex (**127**) is 2 : 1,[98] it was decided to investigate the reaction of lithium-(α-methylbenzyl)benzyl amide (**129**) with the iron crotonyl complex (**127**) (**Scheme 67**).

Scheme 67 : Reaction of lithium-(α-methylbenzyl)benzyl amide (**129**) with the iron crotonyl complex (**127**)



127 **129** **145**

Reactions were performed as detailed in **Tables 8** to **12** in order to establish the stoicheiometry of the various combinations of homochiral and racemic **127** and **129**.

From the results in **Tables 8** and **9**, the observed conversions of starting material (**127**) to product (**145**) show that 2 equivalents of **129** are required to bring about complete reaction of **127**. Therefore the stoicheiometry of the reaction between racemic lithium(α-methylbenzyl)benzyl amide (**129**) and homochiral or racemic iron crotonyl complex (**127**) is 2 : 1. This implies that **129** reacts as a dimer and that once addition has occurred, the unused part of the dimer is unable to return to the reaction medium.

Close examination of the results in **Table 9** reveals that **129** cannot be reacting exclusively as a homochiral dimer, since if it did, when 1 equivalent of *(RS)*-**129** (entry 1) was used, it would imply that 0.25 equivalents of *(R,R)*-dimer and 0.25 equivalents of *(S,S)*-dimer were present in the reaction medium. Thus, when 50% of *(R)*-iron crotonyl

complex (**127**) had been consumed, half (of the 50%) must have reacted with *(R,R)*-dimer to give *(R,R,R)*-product (**145**) and the other half (of the 50%) must have reacted with *(S,S)*-dimer to give a 1 : 1 mixture of *(R,R,S)* and *(R,S,S)*-**145**. This would imply that the overall diastereomeric ratio of the product (**145**) (entry 1 in **Table 9**), would be 50 : 25 : 25 [*(R,R,R)* : *(R,R,S)* : *(R,S,S)*]. As can be seen the value obtained is greatly different from this, thus indicating that **129** cannot be reacting exclusively as homochiral dimers.

Also from **Table 9**, the diastereomeric excesses observed indicate that racemic **129** cannot be reacting as a heterochiral dimer (and that, once addition has occurred, the unused part of the dimer does not return to the reaction medium and reequilibrate to form more reactive dimers). If this were the case, there would be no mass action effect and consequently the expected diastereomeric ratio of the product (**145**) would be the same as that observed in the reaction between racemic **127** and racemic **129** [96 : 2 : 2] as shown in **Table 8**.

Therefore from the results in **Tables 8** and **9**, it appears that the reactive species must be a monomer.

Table 8 : Experiments performed to establish the stoicheiometry of the reaction between lithium[*(RS)*-α-methylbenzyl]benzyl amide (**129**) and *(RS)*-iron crotonyl complex (**127**).

Entry	Equivalents of **129**	% Conversion to product (**145**)[a,b]
1	0.5	29
2	1.0	39, 40
3	1.2	64
4	1.5	74, 75
5	2.0	91
6	2.2	>95
7	2.5	>95
8	4.0	>95

[a] Calculated from NMR spectroscopy of the crude product. [b] Diastereomeric ratio of product calculated by 500 MHz ^{1}H NMR spectroscopy of the crude product = 96 : 2 : 2 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*] in all cases.

Table 9 : Experiments performed to establish the stoicheiometry of the reaction between lithium[*(RS)*-α-methylbenzyl]benzyl amide (**129**) and *(R)*-iron crotonyl complex (**127**).

Entry	Equivalents of **129**	% Conversion to product (**145**)[a]	Diastereomeric ratio of product (**145**)[b]
1	1.0	54	87 : 7 : 6
2	2.0	>90	89 : 6 : 5

[a] Calculated from NMR spectroscopy of the crude product. [b] Diastereomeric ratio of product calculated by 500 MHz ^{1}H NMR spectroscopy of the crude product : [*(R,R,R)* : *(R,R,S)* : *(R,S,S)*].

In contrast, the results in **Tables 10** to **12** show that the stoicheiometry of the reaction between homochiral lithium(α-methylbenzyl)benzyl amide (**129**) and homochiral or racemic iron crotonyl complex (**127**) is 1 : 1 [possibly with the exception of the reaction between the mismatched pair (**Table 12**)]. This implies that homochiral **129** reacts as a monomer, or if homochiral dimers are the reactive species, then in this case, after addition has occurred the unused part of the dimer is able to return to the reaction medium (as a monomer) and reequilibrate to form more reactive dimers.

Table 10 : Experiments performed to establish the stoicheiometry of the reaction between lithium[*(R)*-α-methylbenzyl]benzyl amide (**129**) and *(R)*-iron crotonyl complex (**127**).

Entry	Equivalents of **129**	% Conversion to product (**145**)[a,b]
1	0.5	46
2	0.75	65
3	1.0	86, >95
4	2.2	>95

[a] Calculated from NMR spectroscopy of the crude product. [b] Diastereomerically pure *(R,R,R)* by 500 MHz ^{1}H NMR spectroscopy.

Table 11 : Experiments performed to establish the stoicheiometry of the reaction between lithium[*(R)*-α-methylbenzyl]benzyl amide (**129**) and *(RS)*-iron crotonyl complex (**127**).

Entry	Equivalents of **129**	% Conversion to product (**145**)[a]	Diastereomeric ratio of product (**145**)[b]
1	0.5	48	82 : 9 : 9
2	1.0	>95	55 : 25 : 20

[a] Calculated from NMR spectroscopy of the crude product. [b] Diastereomeric ratio of product calculated by 500 MHz ^{1}H NMR spectroscopy of the crude product : [*(R,R,R)* : *(S,S,R)* : *(S,R,R)*].

Table 12 : Experiments performed to establish the stoicheiometry of the reaction between lithium[*(S)*-α-methylbenzyl]benzyl amide (**129**) and *(R)*-iron crotonyl complex (**127**).

Entry	Equivalents of **129**	% Conversion to product (**145**)[a,b]
1	1.0	58, 61
2	2.2	86

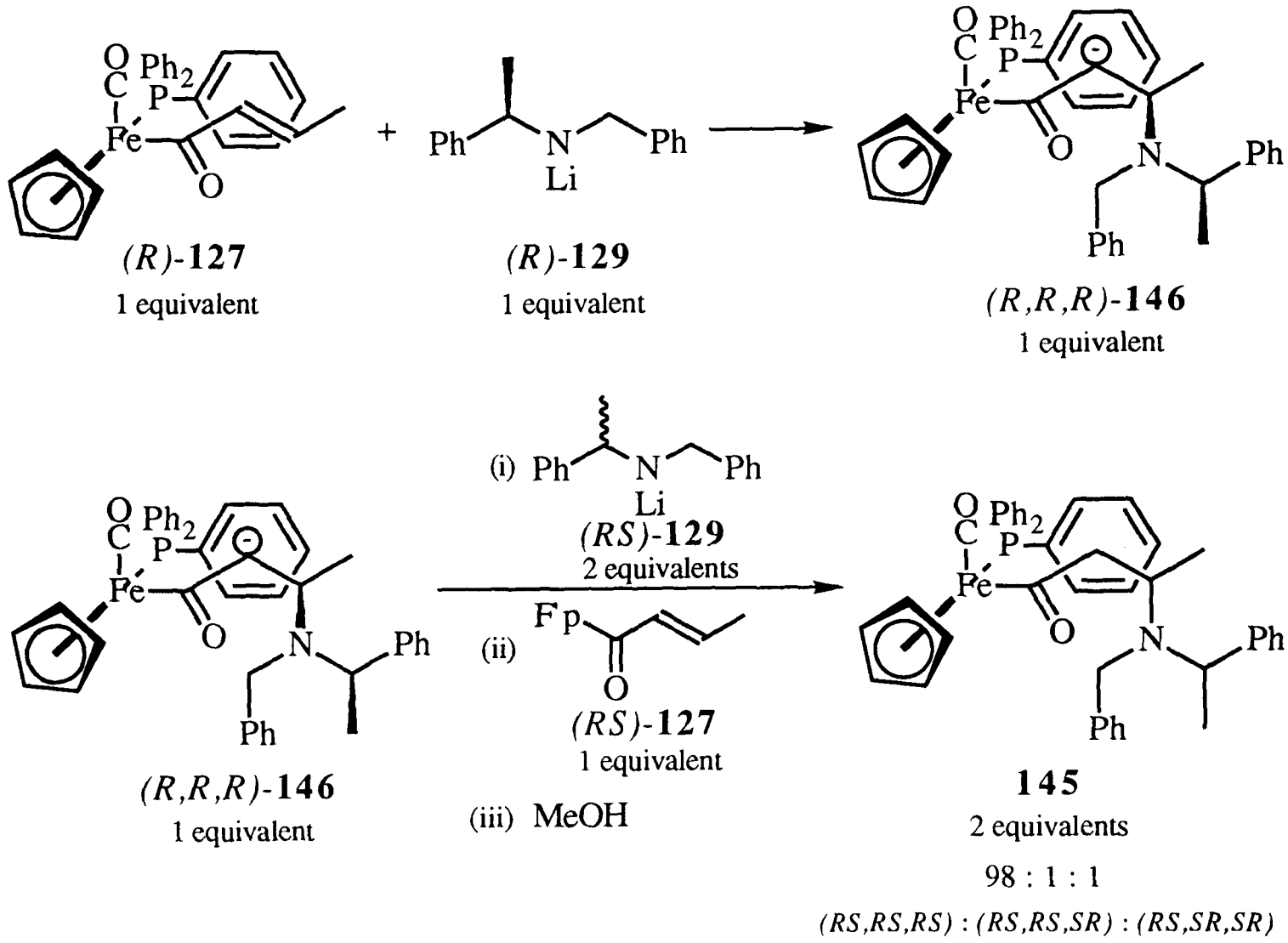
[a] Calculated from NMR spectroscopy of the crude product. [b] 1 : 1 mixture of *(R,R,S)* : *(R,S,S)* by 500 MHz ^{1}H NMR spectroscopy.

It was thought that a possible explanation for the difference in the stoicheiometry of the reactions of homochiral and racemic **129** with **127** was that a chiral recognition process was taking place: if both homochiral and racemic **129** are assumed to be monomeric and the enolate (**146**) formed from reaction of the matched pair [*(R)*-**129** + *(R)*-**127**] is able to chelate selectively to *(S)*-**129** but not to *(R)*-**129**, then the expected stoicheiometries would be the same as those observed experimentally. In order to test this hypothesis the reactions shown in **Schemes 68** to **70** were performed.

In the first experiment (**Scheme 68**) the *(R,R,R)*-enolate of (**146**) was prepared by addition of one equivalent of *(R)*-**129** to *(R)*-**127**. According to the hypothesis outlined above, addition of racemic **129** (two equivalents) would lead to chelation (by **146**) of *(S)*-**129** but not *(R)*-**129**. Therefore when one equivalent of racemic iron crotonyl complex (**127**) was added, it would only be able to react with the one equivalent of *(R)*-amide (**129**) remaining [since *(S)*-**129** had been removed from the reaction medium]. Consequently, the expected overall diastereomeric ratio for the product (**145**) would be 150 : 25 : 25 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*]. If however the

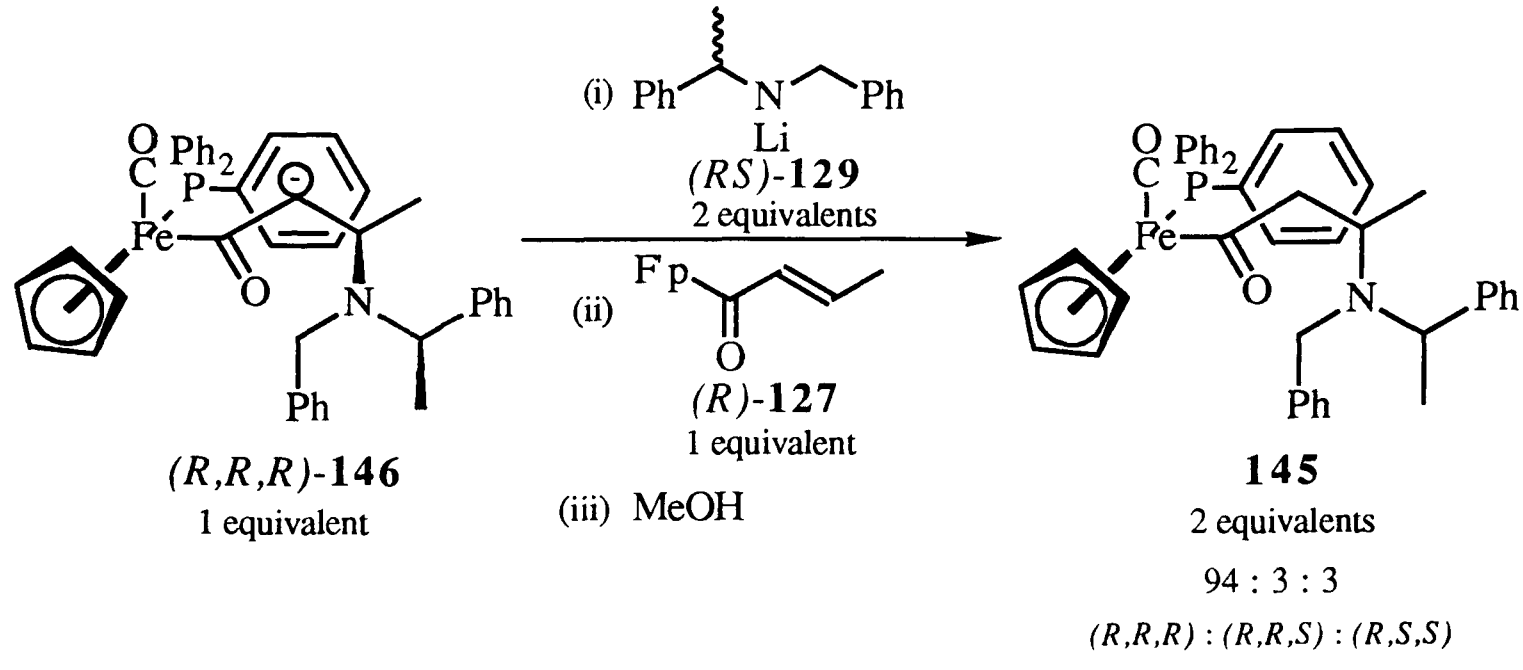
chelation were not occurring, then two equivalents of racemic **129** would be available to react with the one equivalent of racemic **127** added. In which case the expected overall diastereomeric ratio for the product (**145**) would be 196 : 2 : 2 = 98 : 1 : 1 (calculated using data from **Table 8**), which is identical to the ratio observed when the reaction was performed.

Scheme 68 : First experiment performed to test for the occurrence of selective chelation.



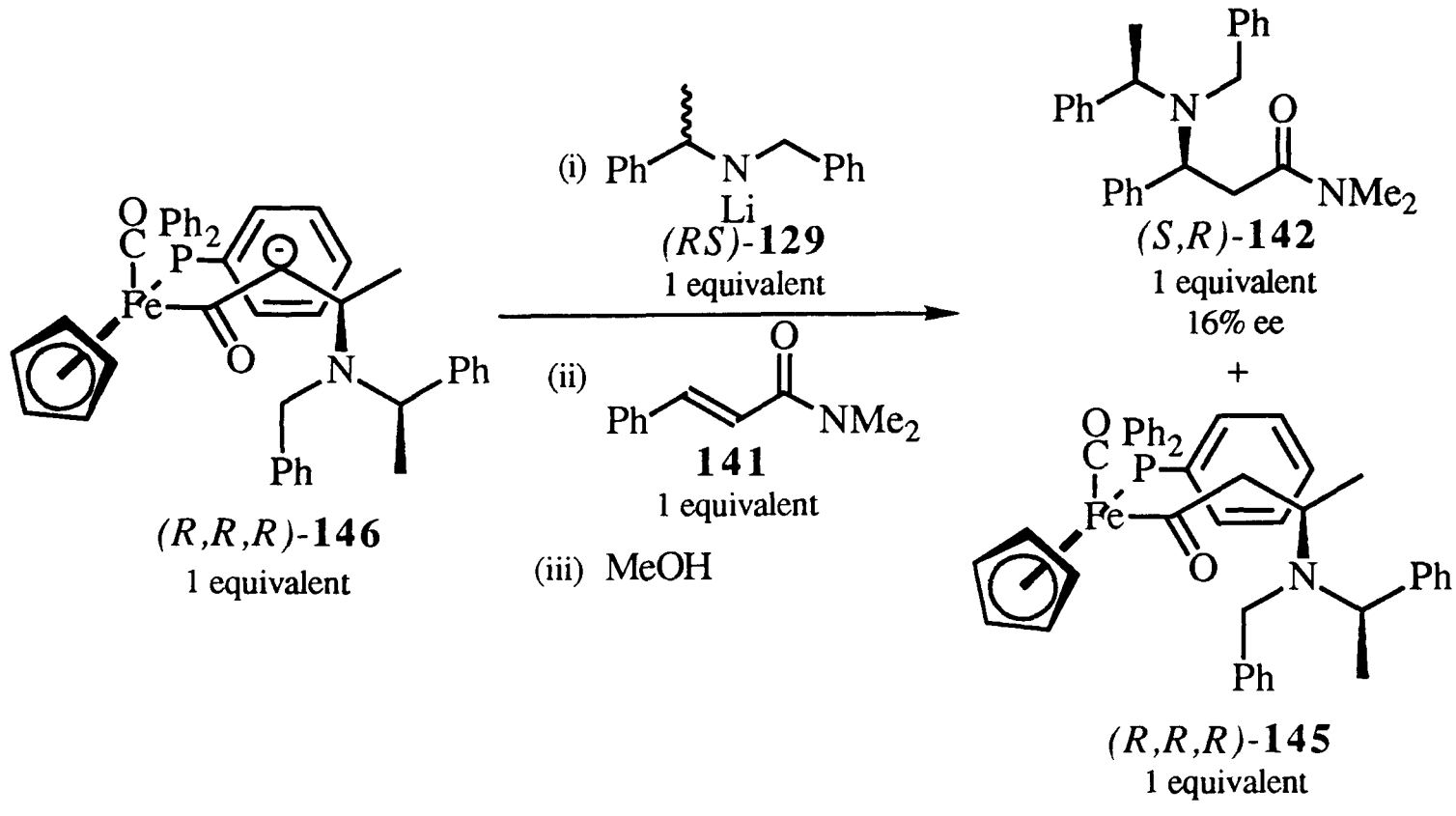
The second experiment (**Scheme 69**) is identical to the first except that *(R)*-**127** rather than racemic **127** was added. In this case, selective chelation would lead to the exclusive formation of the *(R,R,R)*-diastereomer of **145** [since no *(S)*-**129** would be available to react]. If however chelation were not occurring, then two equivalents of racemic **129** would be available to react with the one equivalent of *(R)*-**127** added. In which case the expected overall diastereomeric ratio for the product (**145**) would be 189 : 6 : 5 = 94.5 : 3 : 2.5 (calculated using data from **Table 9**) which again agrees closely with that obtained experimentally.

Scheme 69 : Second experiment to test for the occurrence of selective chelation.



The third experiment (**Scheme 70**) uses the same approach except this time one equivalent of N,N-dimethyl cinnamide (**141**) was added in the second step [rather than the iron crotonyl complex (**127**)]. Here, selective chelation would result in the product from the Michael addition of **129** to **141** being exclusively *(S,R)*-**142** [since no *(S)*-**129** would be available to react], whereas if selective chelation were not occurring, the organic Michael adduct (**142**) would be racemic [*(SR,RS)*]. When the experiment was performed, flash chromatography of the crude product enabled isolation of **142**. Addition of *(R)*-O-acetyl mandelic acid (**144**) to **142** followed by ^{1}H NMR spectroscopy indicated an enantiomeric excess of 16% [enriched in *(S,R)*-**142**]. It was concluded that the slight enantiomeric excess was caused by a small excess of *(R)*-**129** being used in the first step of the reaction and that selective chelation was not occurring.

Scheme 70 : Third experiment performed to test for the occurrence of selective chelation.

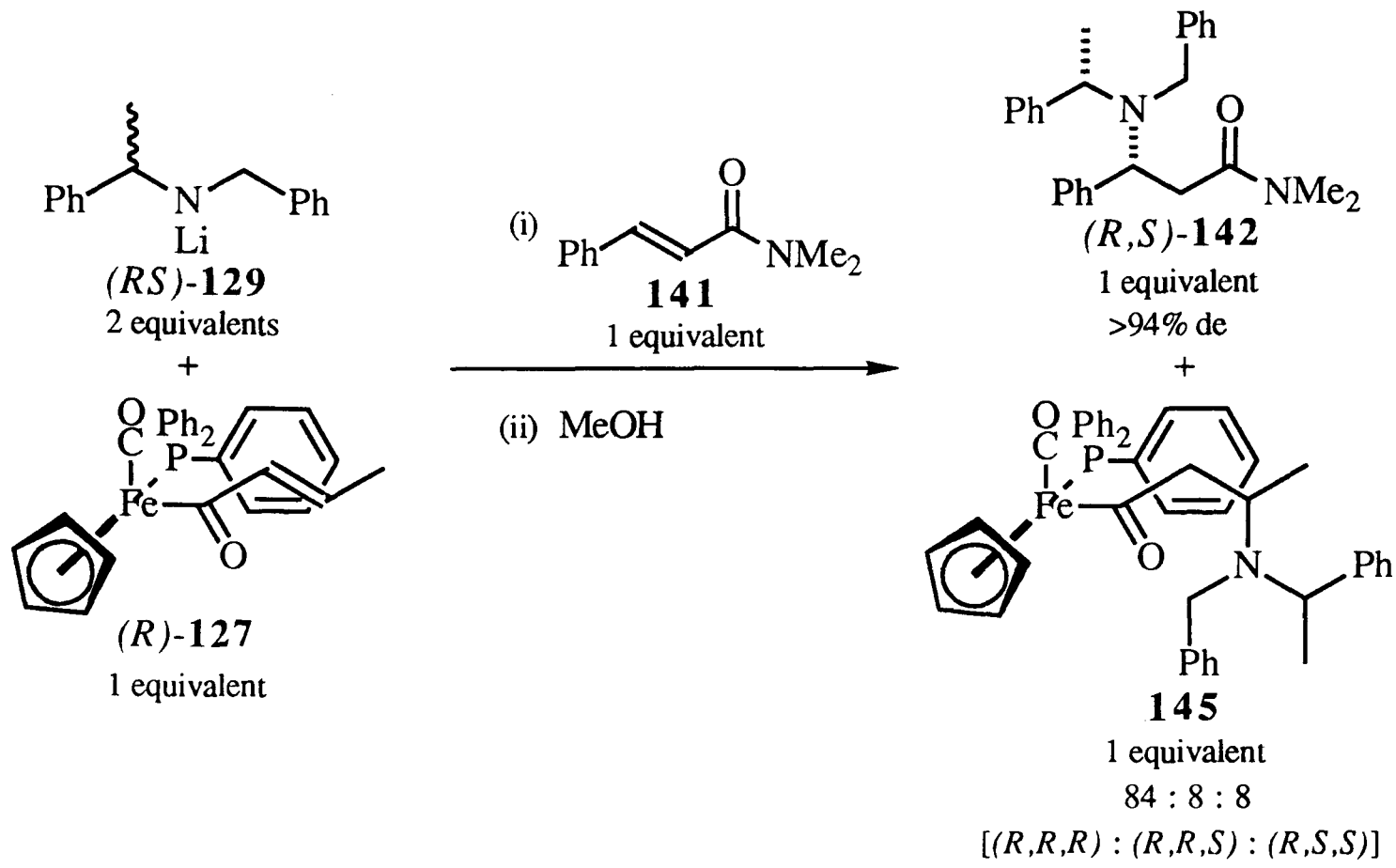


None of the three experiments performed (**Schemes 68** to **70**) was consistent with the proposed selective chelation theory.

Additional experiments were performed as described below.

Reaction of two equivalents of *(RS)*-**129** with one equivalent of *(R)*-**127** was performed. After stirring for 3 h at -78°C, one equivalent of N,N-dimethyl cinnamide (**141**) was added. It was expected that **141** would not undergo any reaction. However after workup, ^{1}H NMR spectroscopy of the crude product revealed that both **127** and **141** had undergone complete conversion to their respective Michael adducts (**145** and **142**). The Michael adducts were formed with the expected (approximately) diastereomeric ratios (**Scheme 71**). As was anticipated, repeating the experiment shown in **Scheme 71** using *(R)*-**129** in place of *(RS)*-**129**, resulted in complete conversion of both **127** and **141**. Therefore it would appear that, in contrast to the iron crotonyl complex (**127**), N,N-dimethyl cinnamide (**141**) is able to breakdown the species that forms between *(R)*-**127** and *(RS)*-**129**.

Scheme 71 : Addition of **141** to the complex formed between *(R)*-**127** and *(RS)*-**129**.



6.4 Summary and Conclusion.

It has been shown that the stoicheiometry of the reaction of racemic or homochiral lithium(α-methylbenzyl)benzyl amide (**129**) with N,N-dimethyl cinnamide (**141**) is 1 : 1. Experiments performed between **129** with a range of enantiomeric excesses and **141** demonstrated that the reaction of **129** and **141** does not display a nonlinear effect. This implies that heterochiral dimers of **129** do not form or if they do form, they react with the same selectivity and the same rate as the monomer or homochiral dimer.

The stoicheiometry of the reaction of racemic lithium(α-methylbenzyl)benzyl amide (**129**) with homochiral or racemic iron crotonyl complex (**127**) is 2 : 1, whereas the stoicheiometry of the reaction of homochiral (**129**) with homochiral or racemic (**127**) is 1 : 1.

In contrast to the iron crotonyl complex (**127**), N,N-dimethyl cinnamide (**141**) is able to breakdown the species that forms between *(R)*-**127** and *(RS)*-**129**.

Measurement of the reaction rate and calculation of the order of reaction with respect to each reactant would provide a very good insight into the mechanism involved. However, due to the reaction proceeding so quickly this is not straightforward.

As yet, no explanation is available that fully accounts for the differing stoicheiometries observed for the reaction of racemic **129** with **127** and the reaction of homochiral **129** with **127**.

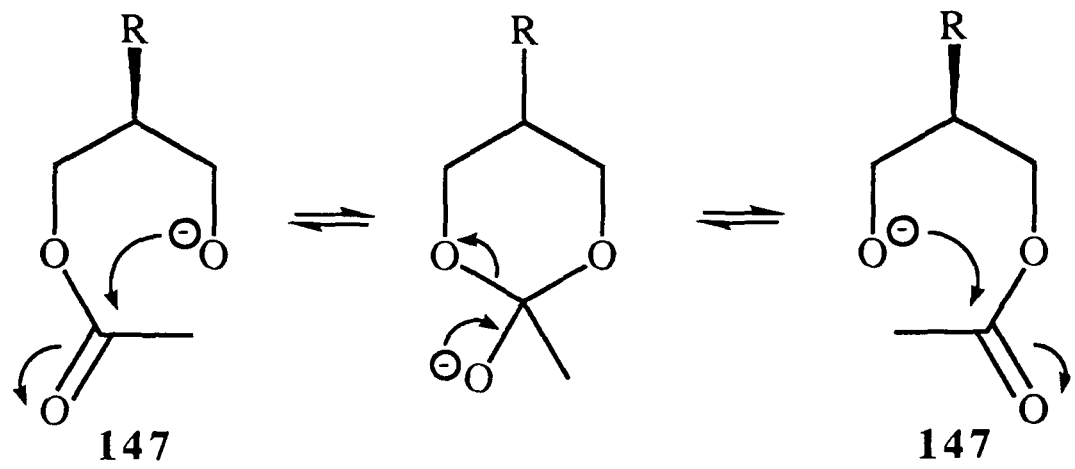
Chapter 7

Attempted Dynamic Kinetic Resolution.

7.1 Proposed Dynamic Kinetic Resolution System.

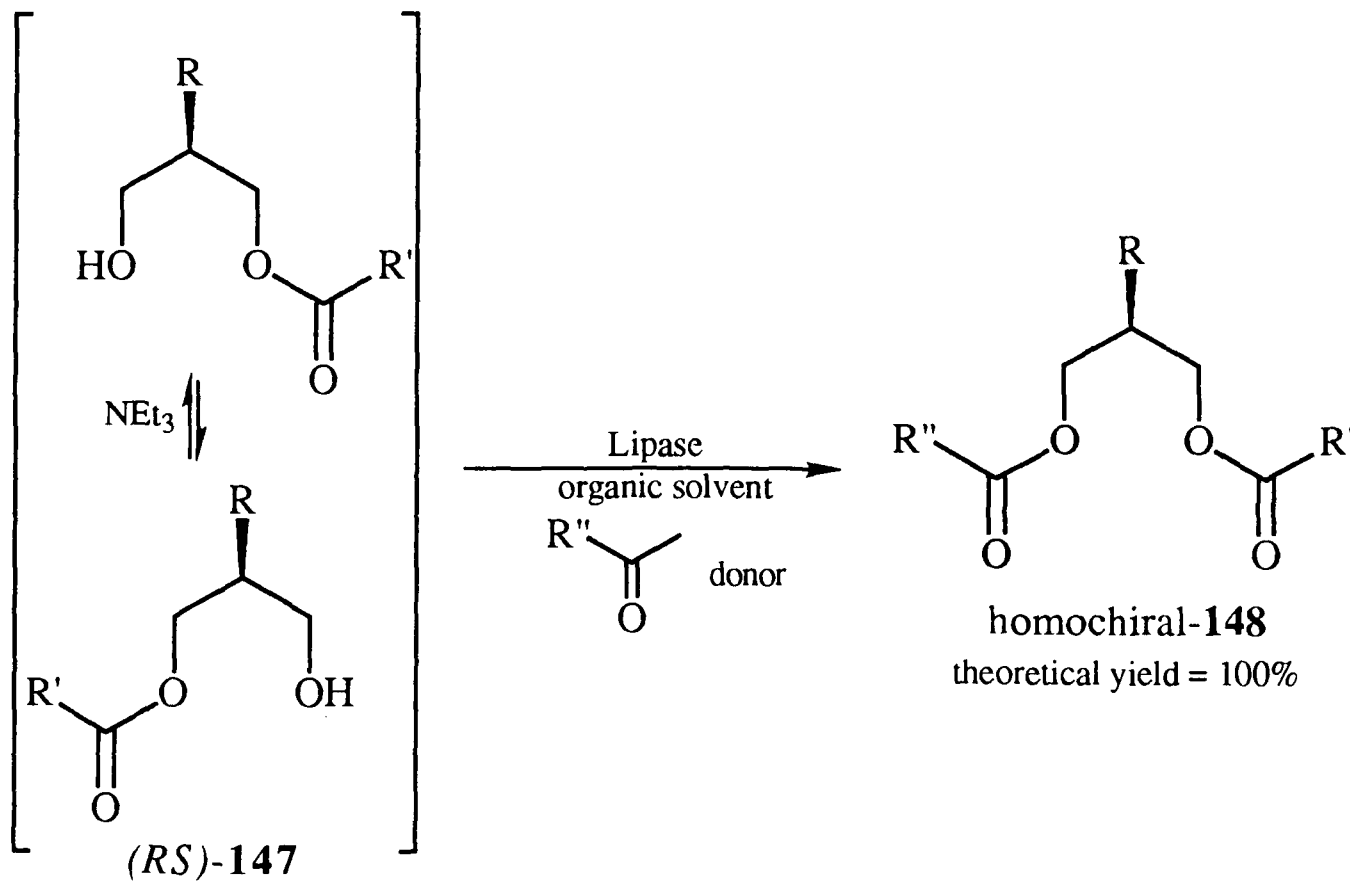
It has been suggested that 2-substituted-1-hydroxy-3-monoacetates (**147**) as shown in **Figure 27** undergo racemisation in the presence of triethylamine *via* an intramolecular 1,3-acetyl transfer process.[69]

Figure 27 : Triethylamine induced scrambling of 2-substituted-1,3-diol derivatives.



It was hoped that a dynamic kinetic resolution could be achieved by coupling this racemisation process with a lipase catalysed selective esterification of the free hydroxyl group to form products as shown in **Scheme 72**.

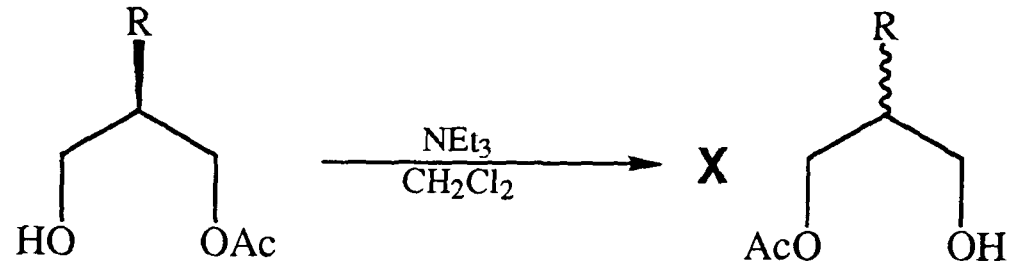
Scheme 72 : Proposed dynamic kinetic resolution.



No problems of incompatibilty between the lipase and triethylamine were envisaged as Thiel *et al.* has demonstrated that a number of lipases readily catalyse transesterification reactions in the presence of triethylamine.[122]

A number of optically active 1,3 diol derivatives (**86, 91** and **149**) were prepared as shown in Chapter 4. However all attempts at racemisation with triethylamine were unsuccessful. In each case the substrate was returned without any decomposition and without any change in its specific rotation (**Scheme 73**).

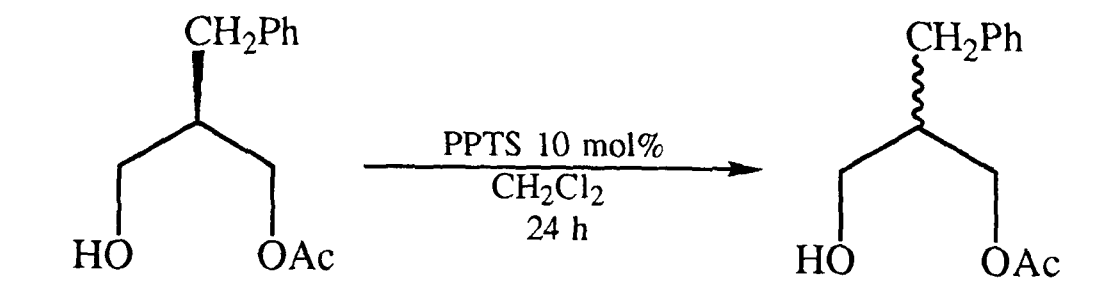
Scheme 73 : Attempted racemisations using triethylamine.



	R	time/h	$[\alpha]_D^{22}$ initial	$[\alpha]_D^{22}$ final
86	CH_2Ph	20	+19	+19 (c = 1.4, $CHCl_3$)
91	CH_2Np	71	+27	+27 (c = 1.0, $CHCl_3$)
149	$CH_2CH(OMe)_2$	18	+11	+11 (c = 1.2, $CHCl_3$)

It was hoped that another racemising agent could be found. Firstly potassium carbonate was tried, without success. Use of 10 mol% pyridinium *para*-toluenesulphonate (PPTS) caused scrambling of the stereogenic centre of **86** after stirring in dichloromethane for 24 h as shown in **Scheme 74**.

Scheme 74 : PPTS mediated racemisation of **86**.



$[\alpha]_D^{22}$ = +19 (c = 1.4, $CHCl_3$)

(R)-(+)-**86**

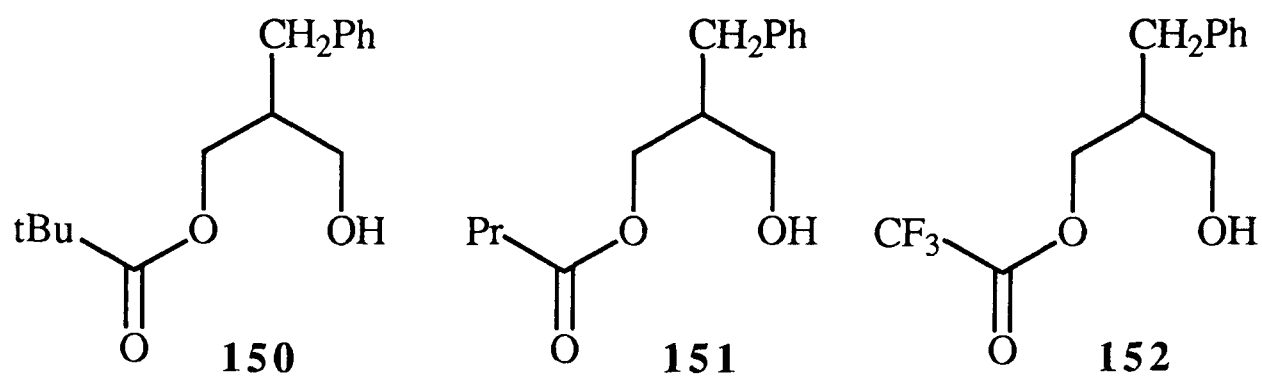
$[\alpha]_D^{22}$ <1 (c = 1.4, $CHCl_3$)

(RS)-(±)-**86**

It was thought that a dynamic kinetic resolution could be performed as proposed in **Scheme 72** by simply replacing triethylamine with PPTS.

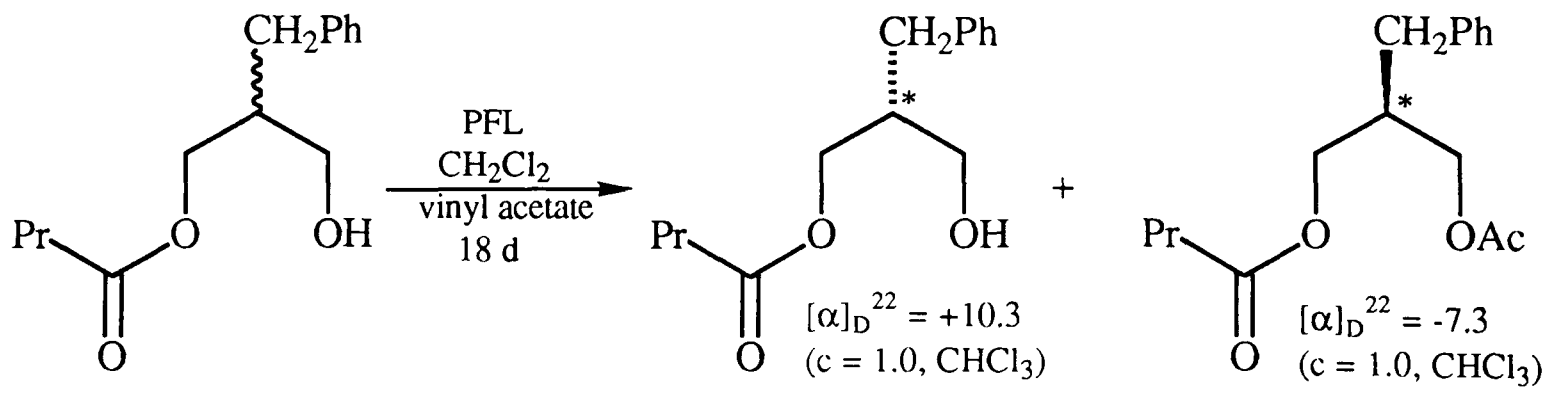
Three novel substrates (**150** - **152**) were prepared and fully characterised (**Figure 28**). The reactivity of *pseudomonas fluorescens* lipase (PFL) towards these substrates was tested.

Figure 28 : Substrates prepared to test the proposed dynamic kinetic resolution system.



The substrates **150** and **152** did not undergo acetylation with PFL, however **151** was readily acetylated to give the novel diester **153** which was fully characterised. After 18 d at room temperature the reaction had proceeded to 38% conversion. The absolute stereochemistry of **153** is unknown, but by analogy with the PFL mediated esterification of 2-benzylpropan-1,3-diol (**85**) (see Chapter 4), it was thought that PFL would preferentially acetylate the *S* enantiomer of **151**. This would lead to formation of the *S* enantiomer of **153** as shown in **Scheme 75**. Unreacted substrate and product were separated by flash chromatography.

Scheme 75 : PFL catalysed acetylation of **151**.



(RS)-(±)-**151**

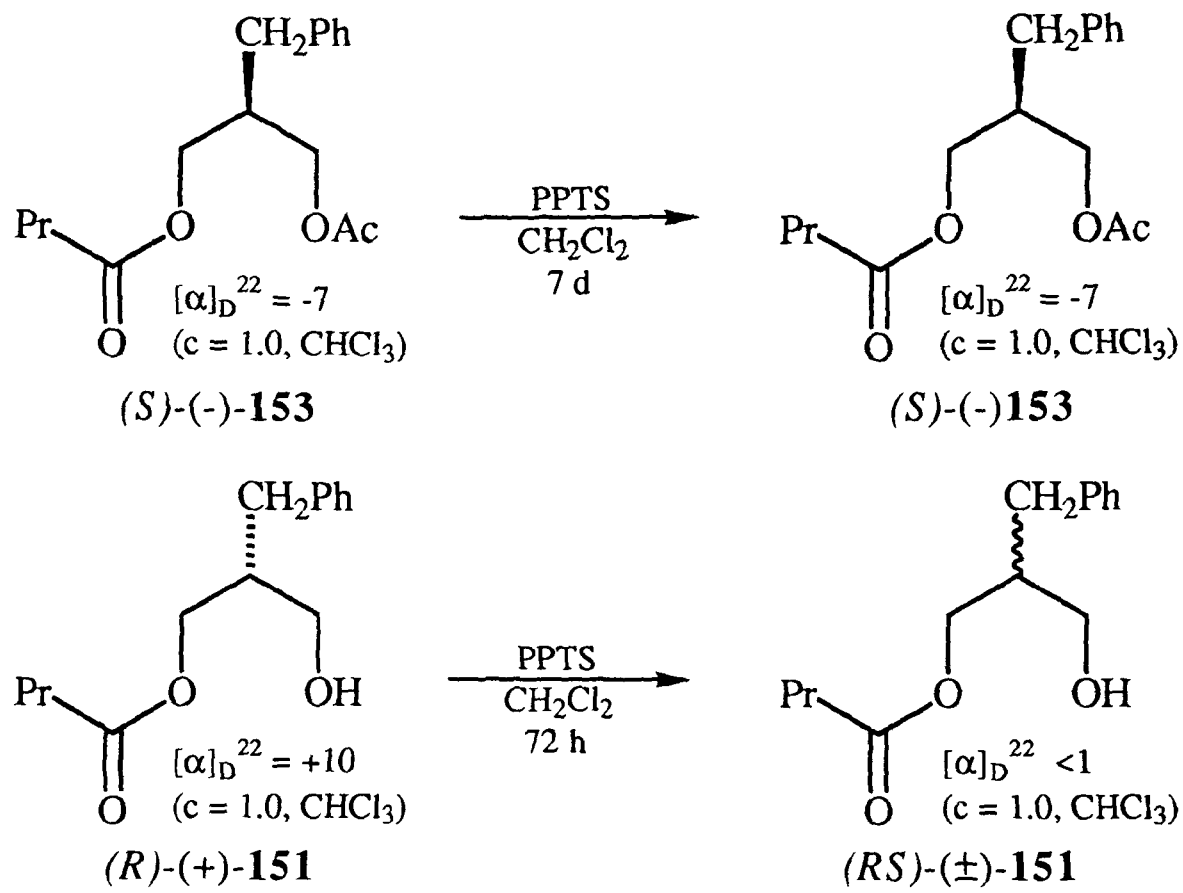
(R)-(+)-**151***

(S)-(-)-**153***

* tentatively assigned

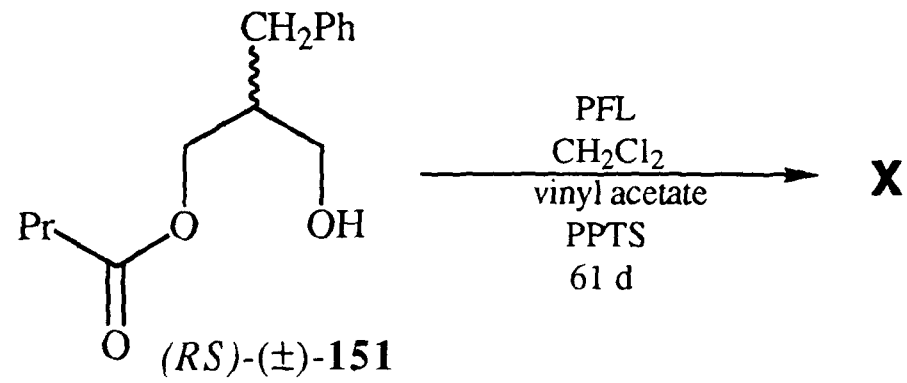
As expected stirring the product from the enzymic acetylation **153** with 10 mol% PPTS in dichloromethane caused no reduction in the optical rotation. Similar treatment of the recovered starting material (**151**) did cause racemisation as detailed in **Scheme 76**.

Scheme 76 : PPTS racemises **151** but does not racemise **153**.



All that remained to be done in order to demonstrate the proposed dynamic kinetic resolution system was to combine the two processes. Frustratingly when the two processes were combined no reaction was observed (**Scheme 77**).

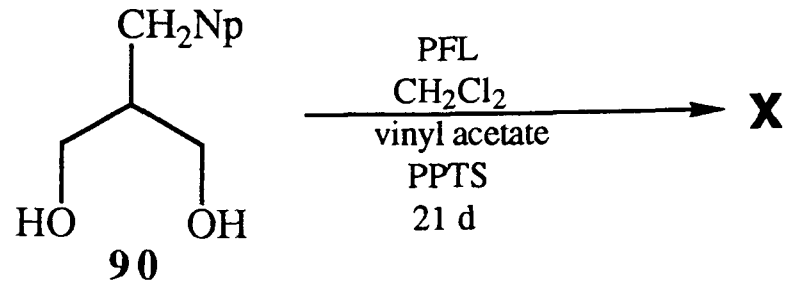
Scheme 77 : Attempted dynamic kinetic resolution.



The most likely explanation is that PPTS inhibits the enzymic reaction. This was confirmed by performing a test reaction with 2-(1-methylnaphthyl)propan-1,3-diol (**90**), a

substrate which is known to be readily acetylated by PFL (see Chapter 4), in the presence of 10 mol% PPTS. Once again no reaction was observed (**Scheme 78**).

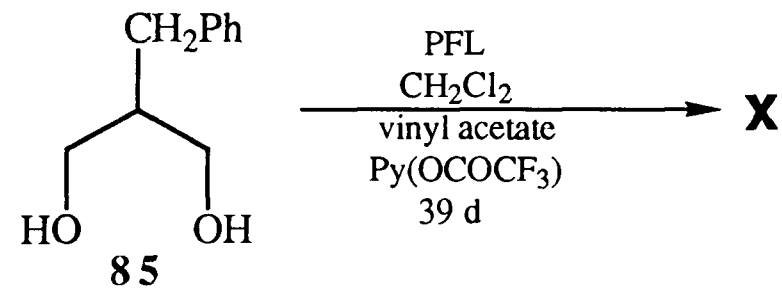
Scheme 78 : Experiment performed to establish if PPTS inhibits PFL.



Experiments were performed to establish if it was the pyridinium moiety or the *para*-toluenesulphonate moiety that was causing the racemisation. Attempted racemisations using tetrabutylammonium *para*-toluenesulphonate [Bu_4N(*p*-TSA)], sodium *para*-toluenesulphonate [Na(*p*-TSA)] and pyridinium trifluoroacetate [Py($OCOCF_3$)] showed that it was in fact the pyridinium moiety that was causing the scrambling of the stereogenic centre.

Unfortunately, PFL was unable to catalyse the esterification of **85** when a pyridinium moiety [this time in the form of Py($OCOCF_3$)] was present (**Scheme 79**). Therefore, it would appear that PFL is inhibited by the presence of a pyridinium moiety. There is evidence in the literature that PFL is also inhibited by species containing an N-methyl imidazole group.[69]

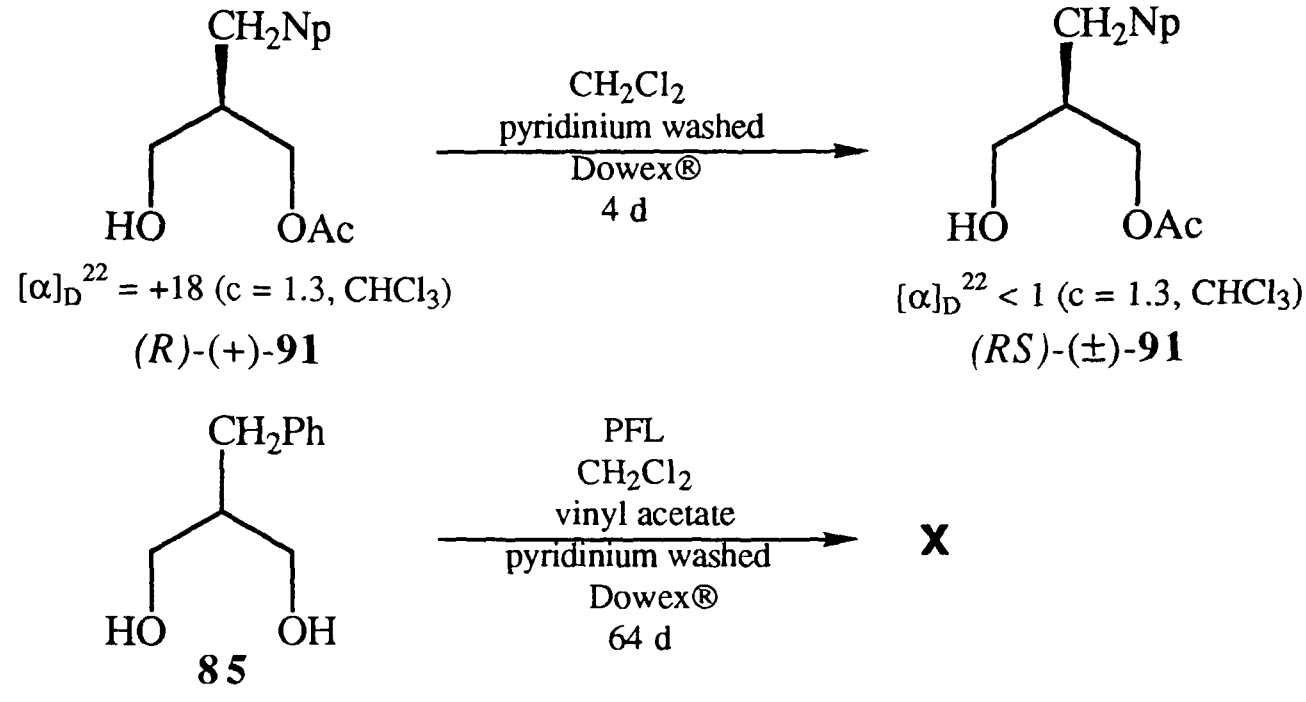
Scheme 79 : Experiment performed to establish if Py($OCOCF_3$) inhibits PFL.



It was hoped that if the pyridinium moiety could be immobilised on a solid support it would still be capable of mediating the racemisation process but would not cause any hindrance to the PFL catalysed esterification.

Successful racemisation was achieved with pyridinium supported on a Dowex® ion exchange resin, however once again, PFL was unable to catalyse esterification reactions in this medium as shown in **Scheme 80**.

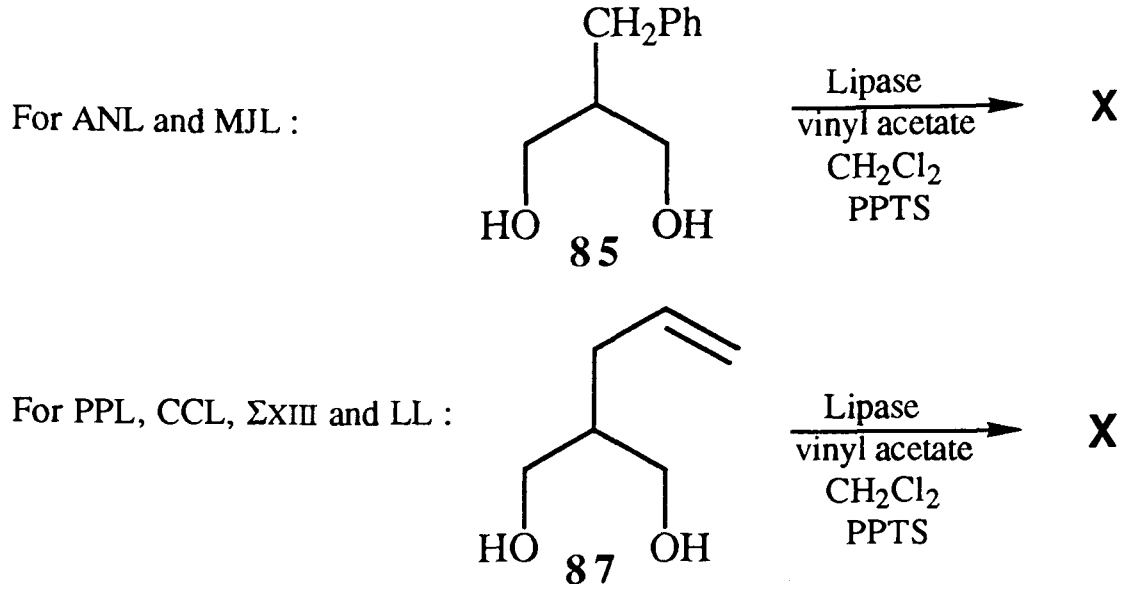
Scheme 80 : Use of Dowex® as an immobilised source of pyridinium ions.



Attempted scrambling using poly(4-vinyl pyridine) was unsuccessful. A number of other racemising agents were tried, including 4-dimethylaminopyridine and 2-hydroxy-pyridine, however in all cases no racemisation was observed.

The next approach tried was to use the proposed dynamic kinetic resolution system as shown in **Scheme 77** with an enzyme other than PFL. A number of readily available lipases were obtained. The compatibility of each enzyme with PPTS was tested by carrying out a known reaction of each enzyme in the presence of 10 mol% PPTS (**Scheme 81**). The enzymes tried were *mucor javanicus* lipase (MJL); *aspergillus niger* lipase (ANL); pig pancreatic lipase (PPL); *candida cylindracea* lipase (CCL); lipase from *pseudomonas* sp. type XIII (ΣXIII) and lipoprotein lipase from *pseudomonas* sp. (LL). Each of the enzymes mentioned was found to be inactive in the presence of PPTS.

Scheme 81 : Incompatibility of various lipases with PPTS.



7.2 Summary and Conclusion

It has been established than 2-substituted-1,3-diol derivatives such as 3-hydroxy-2-benzylpropyl acetate (**86**) undergo racemisation in the presence of a pyridinium moiety whereas unsymmetrical diesters such as 2-benzyl-3-(methylethanoate)propyl butanoate (**153**) are not racemised. 3-Hydroxy-2-benzylpropyl butanoate (**151**) is readily transformed to the diester **153** by *pseudomonas fluorescens* lipase, however 3-hydroxy-2-benzylpropyl trimethylacetate (**150**) and 3-hydroxy-2-benzylpropyl trifluoroacetate (**152**) do not undergo esterification. It has been shown that a number of enzymes are unable to catalyse esterification reactions in the presence of a pyridinium moiety.

The above account is an indication of the magnitude of the obstacles to be overcome in order to perform a dynamic kinetic resolution.

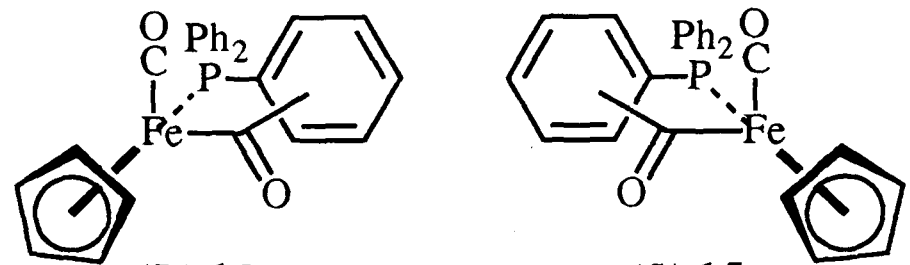
Chapter 8

Attempted Preparation of the Homochiral iron crotonyl complex E-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=CHCH$_3$)] *via* Enzymic Kinetic Resolution.

8.1 Uses of Homochiral iron acyl complexes.

The iron acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COCH_3)]$ (**15**) has been used extensively as a chiral auxiliary by Davies *et al.* for the synthesis of numerous homochiral materials (**Figure 29**).[123]

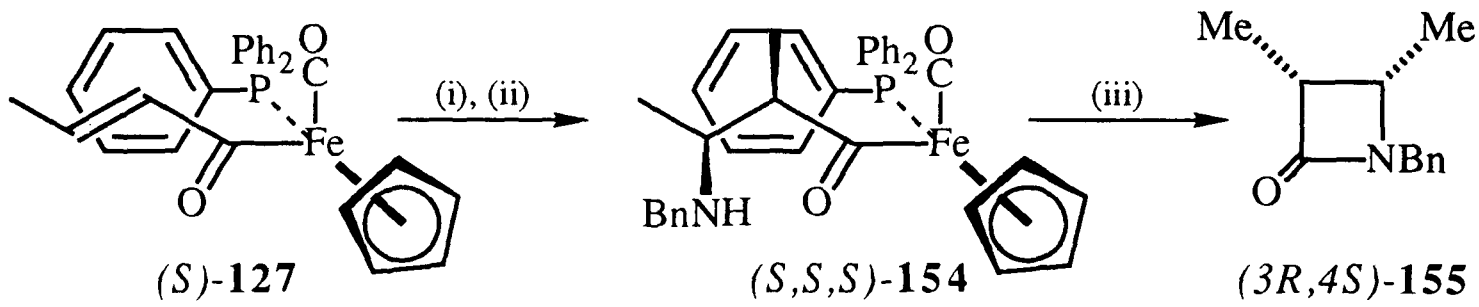
Figure 29 : $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COCH_3)$ (**15**).



(R)-**15** *(S)*-**15**

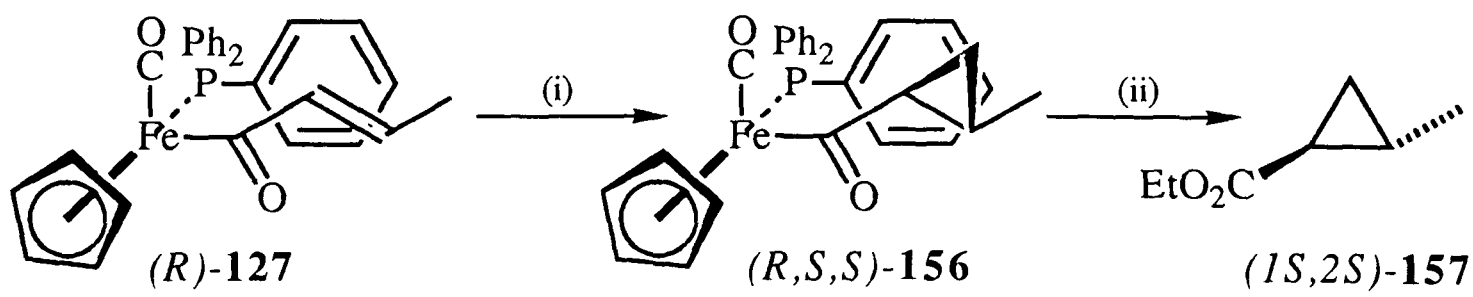
For example, both β-lactams[124] and *trans*-substituted cyclopropane carboxylic acid derivatives[125] have been prepared in homochiral form using the iron crotonyl complex $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COCH{=}CHCH_3)$ (**127**) as a source of chirality (**Scheme 82**).

Scheme 82 : Use of the iron crotonyl complex (**127**).



(S)-**127** *(S,S,S)*-**154** *(3R,4S)*-**155**

(i) BnNHLi. (ii) MeI. (iii) Br_2.



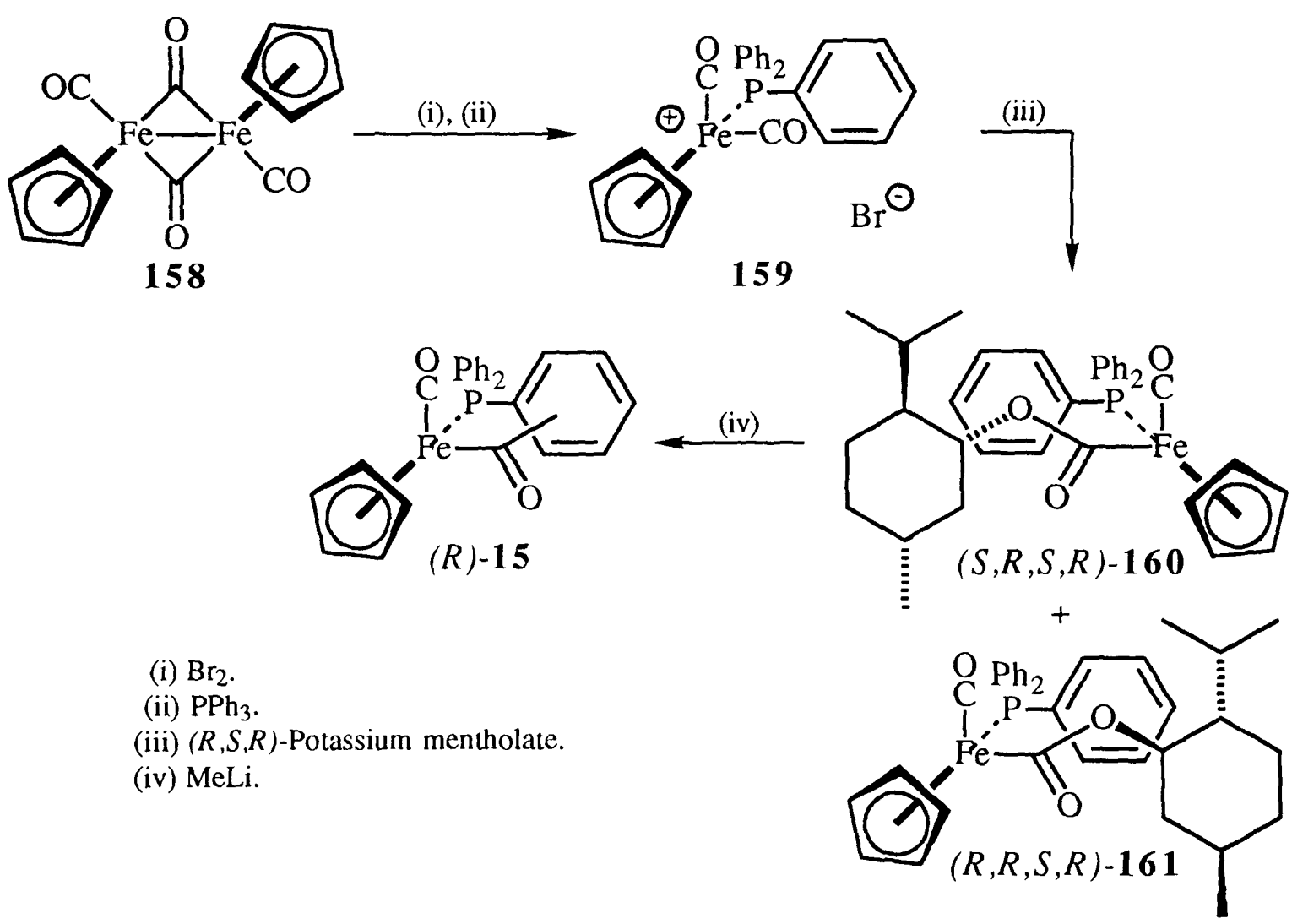
(R)-**127** *(R,S,S)*-**156** *(1S,2S)*-**157**

(i) CH_2I_2, MeLi. (ii) N-bromosuccinnimide, EtOH.

8.2 Methods of Preparing Homochiral iron acyl complexes.

Until recently the only method for the preparation of homochiral (η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**) was as shown in **Scheme 83**. Cleavage of the di-iron species (**158**) with bromine, followed by addition of triphenylphosphine leads to formation of complex **159**. Treatment of **159** with homochiral *(R,S,R)*-potassium mentholate results in the formation of the diastereomers **160** and **161**. Recrystallisation enables isolation of the *S,R,S,R* diastereomer (**160**). Addition of methyllithium to **160** proceeds with inversion (at the iron centre) to give *(R)*-**15**. The *S* enantiomer of **15** can be obtained by use of the opposite enantiomer of potassium mentholate.[126]

Scheme 83 : Preparation of homochiral (η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**).

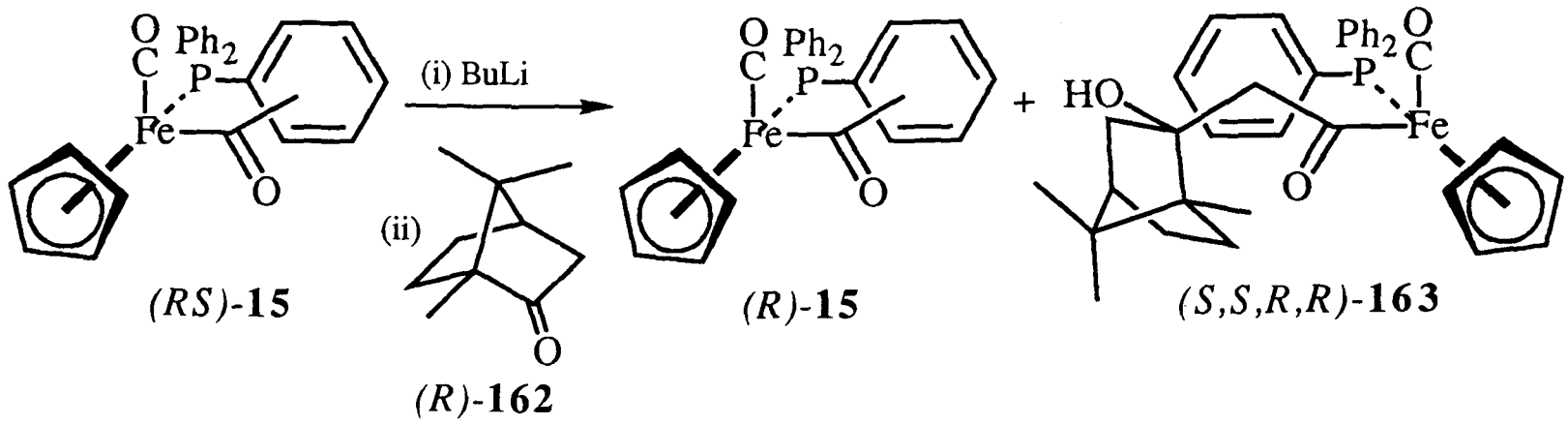


(i) Br_2.
(ii) PPh_3.
(iii) *(R,S,R)*-Potassium mentholate.
(iv) MeLi.

More recently, homochiral (η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**) has been obtained *via* a kinetic resolution process in which the lithium enolate of *(RS)*-**15** undergoes an aldol reaction with homochiral *(1R)*-camphor (**162**). The *S* enantiomer of **15** is

preferentially converted to product (**163**) leaving unreacted **15** enriched in the *R* enantiomer (**Scheme 84**).[127]

Scheme 84 : Kinetic resolution of *(RS)*-(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**) *via* aldol reaction with *(1R)*-camphor (**162**).



Kinetic resolution of iron crotonyl complex *(RS)*-E-(η^5-C_5H_5)Fe(CO)(PPh_3)-($COCH{=}CHCH_3$) (**127**) *via* Michael addition of *(R)*-lithium N-(3,4-dimethoxybenzyl)-α-methylbenzyl amide (**126**) has also been employed as described in Chapter 6.[128]

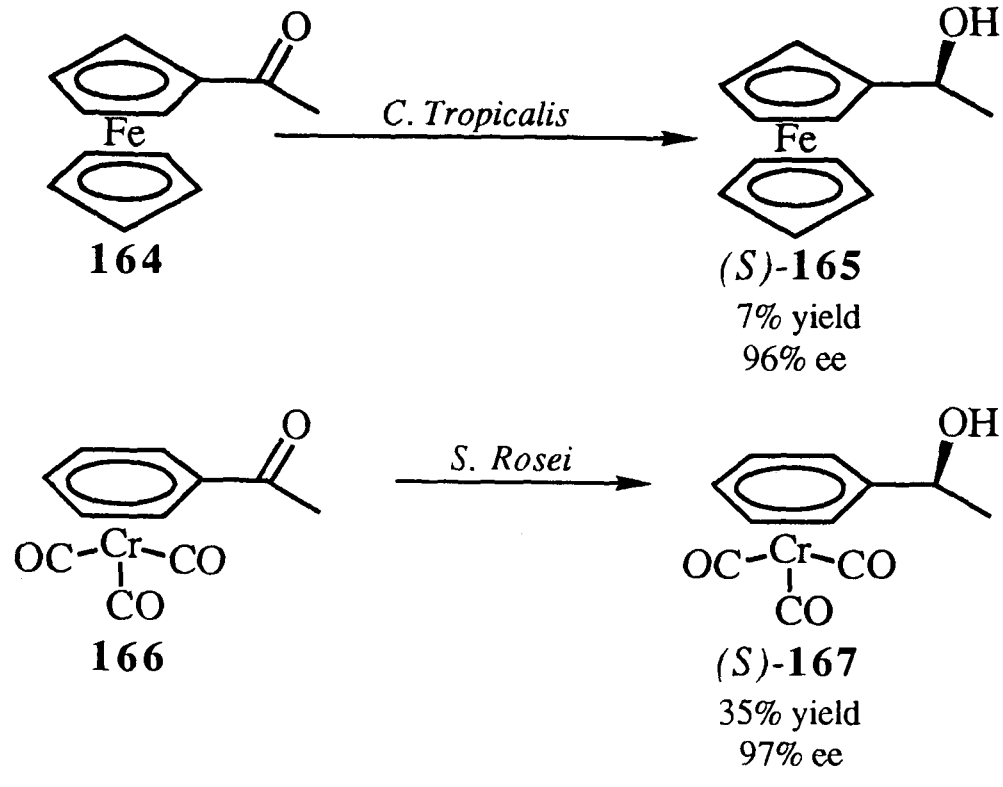
8.3 Preparation of Homochiral Organometallic Complexes using Enzymes.

Enzymic reductions of a number of organometallic complexes have been reported.[129] For example, Yamazaki *et al.* performed the reduction of acetylferrocene (**164**) using *candida tropicalis* to give *(S)*-1-hydroxyethylferrocene (**165**) in 7% yield and with an enantiomeric excess of 96% as shown in **Scheme 85**. Reduction of acetophenone chromium tricarbonyl (**166**) using *sacchraomyces rosei* proceeded to give *(S)*-1-hydroxyethylbenzene chromium tricarbonyl (**167**) in 35% yield and with an enantiomeric excess of >97% (**Scheme 85**).[130]

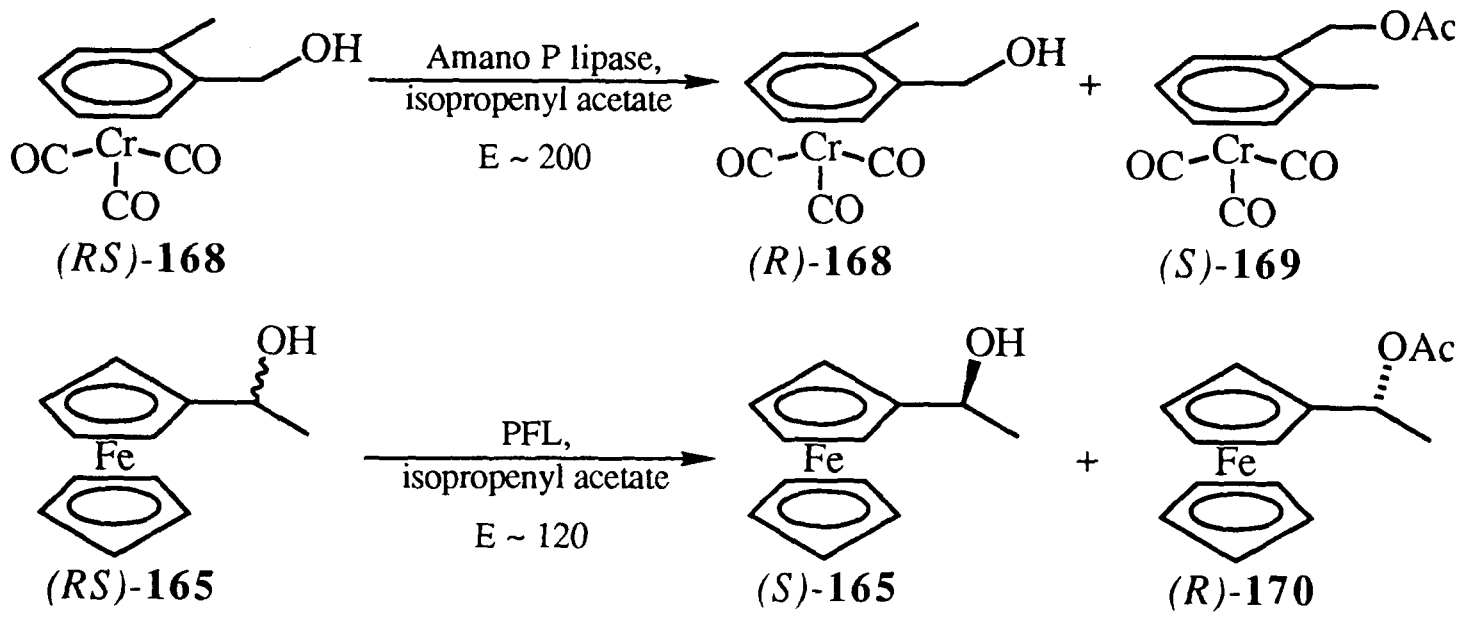
Lipase mediated esterifications and hydrolyses of racemic substrates have been used for the preparation of organometallic complexes in homochiral form. For example, Nakamura *et al.* kinetically resolved *(RS)-ortho*-substituted methylbenzylalcohol chromium tricarbonyl (**168**) in this way using the Amano P lipase (**Scheme 86**). The reaction proceeds with a stereoselectivity factor (E) of ~ 200.[131] Similarly, the PFL mediated kinetic resolution of *(RS)*-1-hydroxyethylferrocene (**165**) has been performed (**Scheme**

86). In this case E ~ 120.[132] Optically active α-hydroxy stannanes and γ-hydroxy vinylstannanes have also been prepared by lipase mediated kinetic resolution.[133]

Scheme 85 : Enzymic reduction of organometallic complexes.



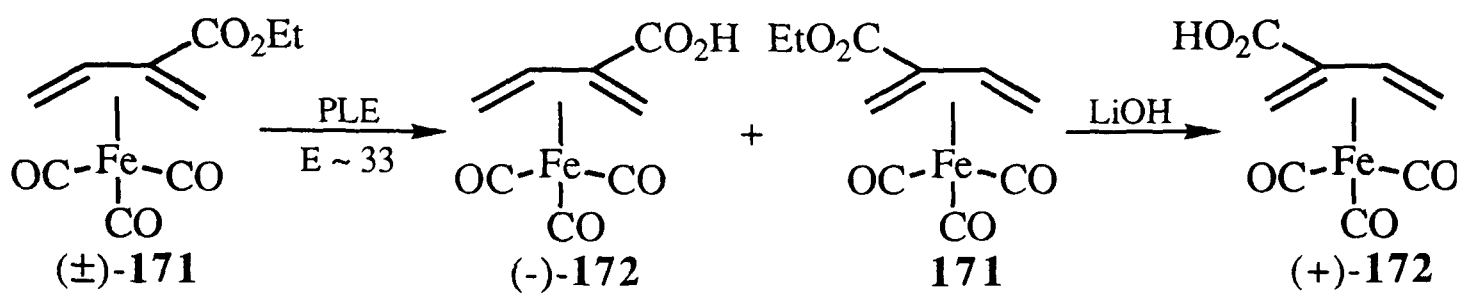
Scheme 86 : Lipase mediated kinetic resolution of organometallic complexes.



The first reported example of enzymic kinetic resolution of an organometallic complex was the pig liver esterase (PLE) mediated hydrolysis of (±)-2-ethoxycarbonylbuta-1,3-diene iron tricarbonyl (**171**) as performed by Crout *et al.* The reaction proceeds with a stereoselectivity factor of approximately 33. Both unreacted **171**

(after chemical hydrolysis to the acid) and the corresponding acid product (**172**) were obtained with >98% enantiomeric excess after one recrystallisation (**Scheme 87**).[134]

Scheme 87 : Enzymic hydrolysis of a buta-1,3-diene iron tricarbonyl complex.

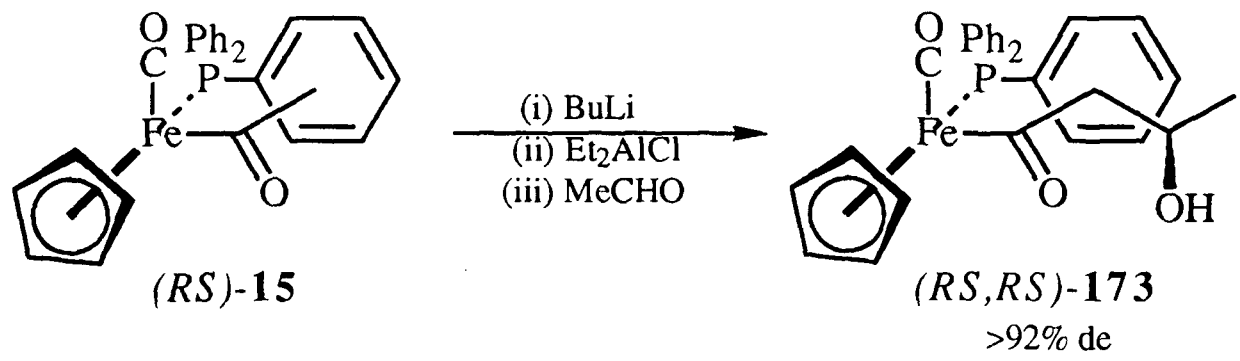


8.4 Proposed Strategy for the Preparation of Homochiral E-[(η^5-C_5H_5)Fe-(CO)(PPh_3)($COCH=CHCH_3$)] (127).

The proposed methodology involved combination of a diastereoselective chemical process with an enantioselective enzymic process as described below.[135]

Aldol reaction of acetaldehyde with the aluminium enolate of *(RS)*-**15** is known to proceed highly selectively to give predominantly the *(RS,RS)*-product diastereomer (**173**) as shown in **Scheme 88**.[136]

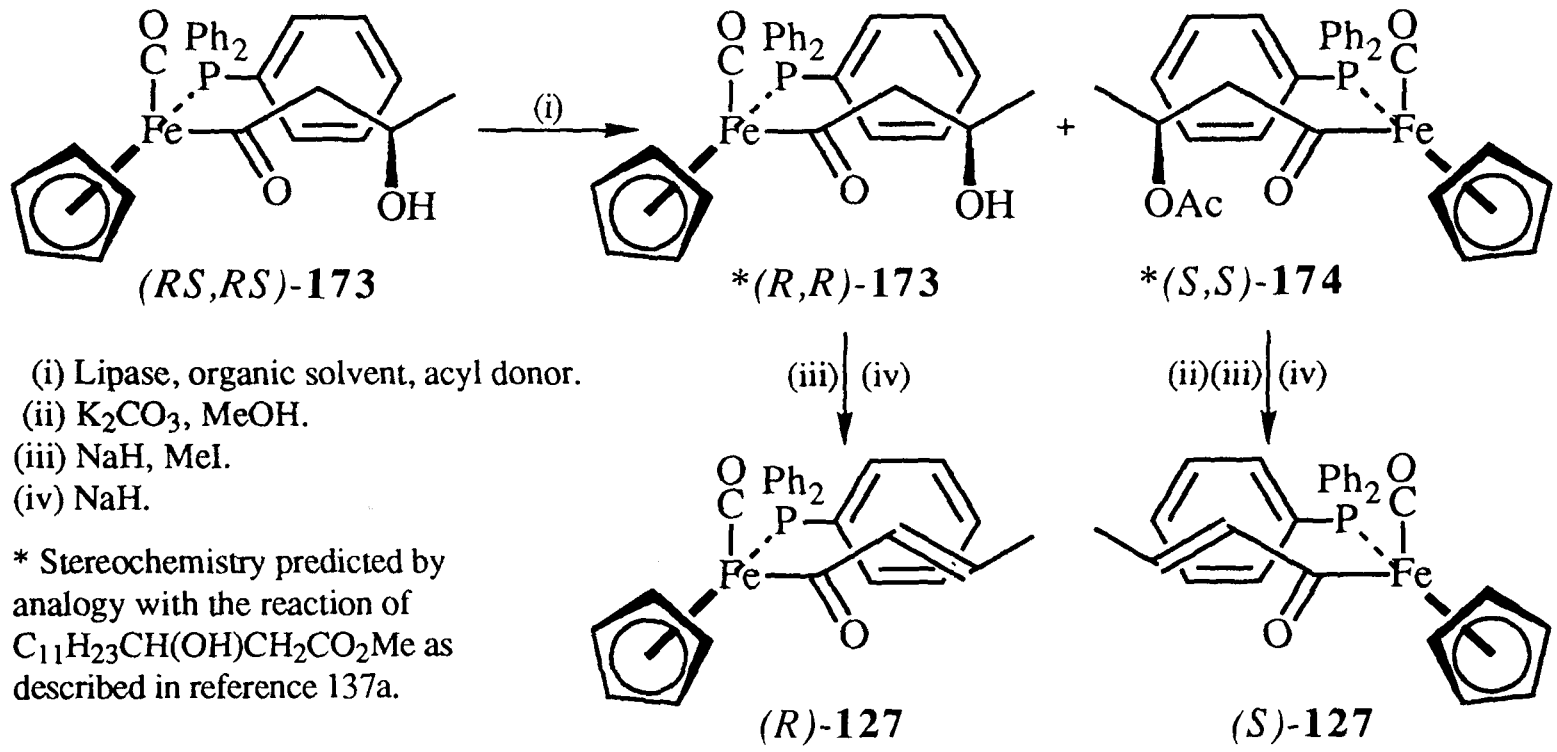
Scheme 88 : Aldol reaction of (η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**) with acetaldehyde.



Since carbonyl compounds containing a β-hydroxy functionality have been shown to be suitable substrates for a number of lipases,[137] it was anticipated that enzymic kinetic resolution of racemic iron complexes such as *(RS,RS)*-**173** would enable formation of homochiral iron complexes (**Scheme 89**). After separation of the expected recovered starting material [*(R,R)*-**173**] and product [*(S,S)*-(**174**], O-methylation of *(R,R)*-**173**

followed by sodium hydride induced elimination of methanol, would lead to formation of the synthetically useful iron crotonyl complex [*(R)*-**127**] in homochiral form (assuming that the resolution was selective).[138] Similar treatment of the product [*(S,S)*-**174**], once it had been hydrolysed to *(S,S)*-**173**, would enable *(S)*-**127** to be obtained. Alternatively, elimination of acetic acid from the product [*(S,S)*-**174**] as described by Liebeskind *et al.* would also lead to the required iron crotonyl complex [*(S)*-**127**] (**Scheme 89**).[139]

Scheme 89 : Proposed enzymic kinetic resolution of racemic *(RS,RS)*-**173** followed by conversion to the iron crotonyl complex (**127**).



(RS,RS)-**173** **(R,R)*-**173** **(S,S)*-**174**

(R)-**127** *(S)*-**127**

(i) Lipase, organic solvent, acyl donor.
(ii) K_2CO_3, MeOH.
(iii) NaH, MeI.
(iv) NaH.

* Stereochemistry predicted by analogy with the reaction of $C_{11}H_{23}CH(OH)CH_2CO_2Me$ as described in reference 137a.

In order to test the viability of the proposed kinetic resolution process, the required starting material *(RS,RS)*-**173** was prepared as described above. A sample of the expected product *(RS,RS)*-(**174**) was prepared according to the literature procedure.[140] After stirring *(RS,RS)*-**173** in dichloromethane for 17 d with *pseudomonas fluorescens* lipase (PFL) using vinyl acetate as acyl donor, no trace of product was observable by TLC or ^1H NMR spectroscopy.

It was thought that use of the other diastereomer of **173** [*(RS,SR)*] may prove more successful. Consequently, the aldol reaction of the lithium enolate of **15** was performed with acetaldehyde. This produced an approximately 1 : 1 mixture of *(RS,RS)*-**173** and *(RS,SR)*-**173**. If it was found that enzymic esterification occurred with the

(RS,SR) diastereomer, aldol reaction between the copper or tin enolate of **15** and acetaldehyde would allow selective formation of the *(RS,SR)* diastereomer of **173**.[138] After enzymic resolution of *(RS,SR)*-**173**, conversion of the expected recovered starting material [*(S,R)*-**173**] and the expected product [*(R,S)*-**174**] to the required iron crotonyl complex (**127**) could be performed using the same conditions as shown in **Scheme 89** for *(R,R)*-**173** and *(S,S)*-**174** respectively.

Enzymic esterification of the 1 : 1 mixture of diastereomers was attempted with a number of lipases using vinyl acetate or isopropenyl acetate as the acyl donor. Reactions were performed using dichloromethane as solvent or in neat vinyl acetate or isopropenyl acetate. The enzymes screened were *aspergillus niger* lipase; *candida cylindracea* lipase; lipoprotein lipase from *pseudomonas* sp.; *mucor javanicus* lipase; pig pancreatic lipase (PPL); PFL; lipase from *pseudomonas* sp. type XIII and *rhizopus arrhizus* lipase. After a typical reaction time of 15 - 20 d, the only experiment that had shown any sign of reaction was that using PPL. Therefore, reaction of diastereomerically pure *(RS,RS)*-**173** was tried with PPL. Once again a second spot was observed on TLC. The reaction mixture was filtered to remove the enzyme, and solvent was removed *in vacuo* to yield the crude product. Flash chromatography enabled separation of product and starting material (**173**). Only a very small amount of product was obtained, and all attempts at identification proved unsuccessful. Measurement of the specific rotation of the product and the recovered starting material (**173**) revealed no optical activity.

8.5 Summary and Conclusion.

From the experiments performed it has been found that β-hydroxy iron complexes are not suitable substrates for a number of readily available lipases. Judging by the fact that lipases have been shown to be capable of mediating esterifications of a range of organometallic complexes, it is thought that the most likely cause of the unsuitability is the presence of the sterically demanding $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)$ substituent.

General Experimental

General Experimental Techniques.

Solvents

Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Diethyl ether and toluene were dried over sodium wire. Petrol refers to that fraction of petroleum ether that boils between 40°C and 60°C unless otherwise stated.

Reagents

Butyllithium was used as a 1.6 M solution in hexanes. Sodium hydride was washed with petrol (3 x 20 mL) and then dried *in vacuo* before use. Triethylamine was distilled and stored over potassium hydroxide pellets. Other reagents were used as received or purified according to standard methods.[141]

Enzymes

The following enzymes were used:

Aspergillus niger lipase	ANL	Fluka 62301
Candida cylindracea lipase	CCL	Sigma L1754
Lipase from *pseudomonas* sp. type XIII	ΣIII	Sigma L9518
Lipoprotein lipase from *pseudomonas* sp.	LL	Fluka 62335
Mucor javanicus lipase	MJL	Fluka 62304
Pig pancreatic lipase	PPL	Sigma L3126
Pseudomonas fluorescens lipase	PFL	Fluka 62312
Rhizopus arrhizus lipase	RAL	Fluka 62305
Saccharomyces cerevisiae (Baker's yeast)		Sigma YSC-2

pH Stat

Enzymic hydrolyses were performed using a Radiometer RTS822 autotitration system.

General

All Sharpless epoxidations and all experiments that involved the use of iron complexes, lithium amides, metal hydrides or alkyl halides were performed under a nitrogen atmosphere using degassed solvents and standard vacuum line and Schlenk techniques.[142]

Chromatography

Flash chromatography was performed on silica gel (40 - 60 μm) or on grade V alumina. Chromatography of iron complexes was performed under a nitrogen atmosphere.

Thin layer chromatography was carried out using aluminium sheets precoated with Merck Kieselgel $60F_{254}$ silica gel or Macherey-Nagel plastic backed alumina plates (802022).

Gas chromatography was performed using a Carlo-Erba instrument fitted with a 25 m BP10 capillary column and a flame ionisation detector.

High performance liquid chromatography was performed using a Waters instrument fitted with a variable wavelength detector. The column used is described in the relevant section of the experimental.

Mass Spectrometry

Mass spectra were recorded on a VG Micromass ZAB1F or a TRIO-1 GC-MS instrument using either fast atom bombardment, electron impact or chemical ionisation techniques.

NMR Spectroscopy

^{1}H NMR spectra were recorded on a Varian Gemini 200 operating at 200 MHz, a Bruker WH300 at 300 MHz or a Bruker AM500 spectrometer at 500 MHz. ^{13}C NMR spectra were obtained on a Bruker AM250 at 62.9 MHz or on a Varian Gemini 200 spectrometer at 50.3 MHz. ^{31}P and ^{19}F NMR spectra were recorded on a Bruker AM250 spectrometer at 101.26 MHz and 235.35 MHz respectively. All samples were run in

deuteriochloroform unless otherwise stated. ^{1}H and ^{13}C samples were referenced to tetramethylsilane using the signal from residual protio solvent. ^{19}F samples were referenced externally to $CFCl_3$. ^{31}P samples were referenced externally to 85% *ortho*-phosphoric acid. Chemical shifts quoted for ^{13}C and ^{31}P are from the broad band proton decoupled spectra.

Infrared Spectroscopy

Infrared spectra were run as chloroform solutions on a Perkin-Elmer 781 or a Perkin-Elmer 1750 spectrometer.

Elemental Analyses

Elemental microanalyses were performed by Mrs. V. Lamburn at the Dyson Perrins Laboratory.

Optical Rotations

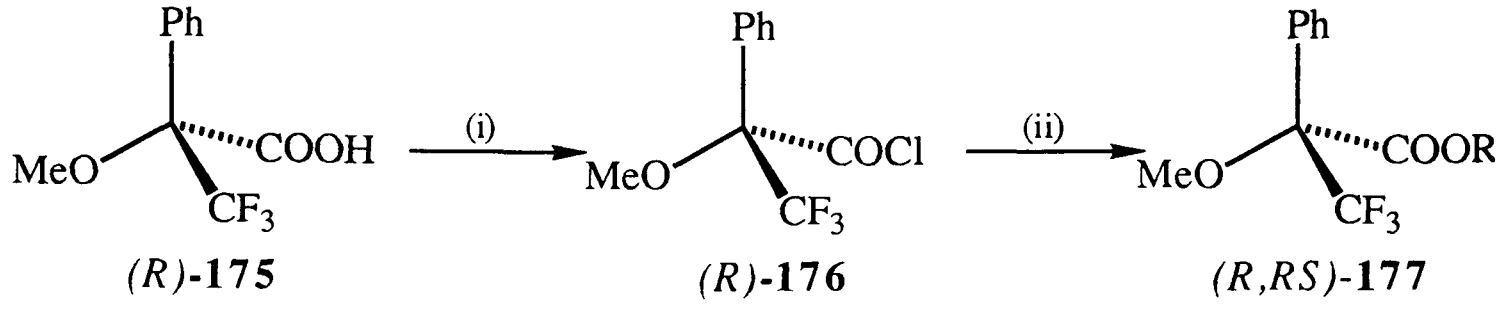
Optical rotations were measured using a Perkin-Elmer 241 polarimeter in various solvents at 22°C.

General Procedure for the preparation of α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) esters.[46]

A solution of (*R*)-(+)-MTPA (**175**) (23 mg, 0.1 mmol) in toluene (2 mL) was treated with oxalyl chloride (16 μL, 0.2 mmol) and DMF (~ 0.05 mL). The reaction mixture was stirred for 30 min at room temperature. Solvent and excess oxalyl chloride were then removed *in vacuo* to give the acid chloride of MTPA (**176**). CH_2Cl_2 (5 mL) was added and the solution was used immediately. The alcohol to be derivatised (0.1 mmol) in CH_2Cl_2 (5 mL) was treated with DMAP (5 mg), triethylamine (66 μL, 0.2 mmol) and the solution of MTPA acid chloride (**176**) (**Scheme 90**). The reaction was monitored by TLC. When all the alcohol had been consumed, N,N-dimethylaminoethanol (0.1 mL) was added and the solvent was removed *in vacuo*. The residue was dissolved in 1 : 4,

Et_2O : petrol and filtered through an alumina (grade V) plug. Removal of solvent yielded the MTPA ester of the alcohol (**177**) as a colourless oil. Normally, further purification was not required however in some cases flash chromatography was performed on silica with Et_2O : petrol mixtures as eluant.

Scheme 90 : Preparation of Mosher's ester derivatives.



(R)-**175** *(R)*-**176** *(R,RS)*-**177**

(i) $(COCl)_2$, DMF, toluene.
(ii) ROH, NEt_3, DMAP, DMAE, CH_2Cl_2.

General Procedure for enzyme catalysed acetylation reactions.

Vinyl acetate (2.0 equivalents) and the appropriate enzyme were added to a solution of the substrate in CH_2Cl_2. The mixture was stirred at room temperature. The extent of the reaction was monitored by removal of an aliquot followed by TLC or ^1H NMR analysis. When the reaction had proceeded to the required conversion, filtration of the reaction mixture (to remove the enzyme) followed by removal of solvent and excess vinyl acetate *in vacuo* yielded the crude product. ^1H NMR of the crude product enabled accurate calculation of the conversion. Flash chromatography (silica, Et_2O : petrol mixtures) was used to separate products from recovered starting material.

General Procedure for enzymed catalysed hydrolysis reactions.

The substrate and appropriate enzyme were added to pH 7 phosphate buffer (10 mL) and the reaction mixture was stirred at room temperature. The pH of the reaction was maintained by the use of an autotitrator dispensing 1N NaOH solution. Extent of reaction was monitored by reference to the amount of NaOH added. Reaction was halted at the required conversion by repeated extraction with CH_2Cl_2 or EtOAc. After drying ($MgSO_4$) and filtration, removal of solvent *in vacuo* yielded the crude product. ^1H NMR of the

crude product enabled accurate calculation of the conversion. Flash chromatography (silica, Et_2O : petrol mixtures) was used to separate products from recovered starting material.

Analytical Data.

All novel compounds were fully characterised (including elemental analysis).

For all known compounds, ^1H NMR data has been quoted and a literature reference has been given. In all cases the ^1H NMR data obtained was very similar to the data quoted in the literature reference.

Chapter 2

Experimental

Preparation of a dichloromethane solution of *t*-butylhydroperoxide (TBHP).

A dichloromethane solution of TBHP was prepared as described in reference 143. The molarity of the solution was measured using ^1H NMR spectroscopy and found to be 3.6 M.

Measurement of the enantiomeric excesses of 48 and 49.

After preparation of Mosher's ester derivatives as described in the General Experimental, ^{19}F NMR spectroscopy was performed. For the allylic alcohol (**48**), signals were observed at ~ -73.5 [*(R)*-**48**] and at ~ -73.9 ppm [*(S)*-**48**]. Signals for the epoxide product (**49**) were observed at ~ - 73.7 [*(R,R,S)*-**49**] and at ~ -73.9 ppm [*(S,S,R)*-**49**].

Sharpless epoxidation of racemic 3-methylcyclohex-2-en-1-ol (48): first step of double kinetic resolution.

To a stirred solution of 3-methylcyclohex-2-en-1-ol (**48**) (2.00 g, 17.8 mmol), (+)-DiPT (0.63 g, 2.7 mmol), nonane (~ 1.0 mL) and molecular sieves (4Å) in CH_2Cl_2 (50 mL) at -23°C was added $Ti(OiPr)_4$ (0.5 mL, 1.7 mmol). An aliquot of the reaction mixture was removed and treated as described below so that the extent of the reaction could be monitored. After stirring for 2 h (catalyst conditioning), TBHP [3.5 mL (of a 3.6 M CH_2Cl_2 solution), 12.6 mmol] was added. After stirring for a further 4 h at -23°C, GLC (as described below) indicated that the reaction had proceeded to the desired 58% conversion. Standard non-acidic workup[45] was performed as follows: a solution of NaOH (30% w/v) in saturated brine (3 mL) and Et_2O (10 mL) were added and the reaction mixture was warmed to room temperature, then $MgSO_4$ (2 g) and celite (0.5 g) were added. Stirring for 15 min filtration and removal of solvent *in vacuo* yielded the crude product as a yellow oil. Flash chromatography was performed (silica, 2 : 1, Et_2O : petrol) and yielded recovered starting material [*(R)*-**48**] (0.62 g, 31%) {$[\alpha]_D^{22}$ = +66.2 (c = 0.9, $CHCl_3$), literature [*(S)*-**48**][47]: $[\alpha]_D^{20}$ = -96.3 (c = 0.5, $CHCl_3$)} and product [*(S,S,R)*-**49**] (0.94 g, 41%) {$[\alpha]_D^{22}$ = -35.8 (c = 1.0, $CHCl_3$)} as colourless oils. Enantiomeric excesses were

measured as described above, **48** was obtained with an enantiomeric excess of 69%, and **49** was obtained with an enantiomeric excess of 50%. The recovered reactant (**48**) was used as starting material in a second kinetic resolution as described below.

48[47] : δ_H 5.49 [1H, s, CHOHC<u>H</u>], 4.17 [1H, s br, C<u>H</u>OH], 1.69 [3H, s, C<u>H</u>$_3$], 2.0 - 1.2 [7H, m, (C<u>H</u>$_2$)$_3$ + O<u>H</u>].

49[144] : δ_H 4.01 [1H, m, C<u>H</u>OH], 3.16 [1H, d, J 3 Hz, CHOHC<u>H</u>], 1.35 [3H, s, C<u>H</u>$_3$], 2.2 - 1.2 [7H, m, (C<u>H</u>$_2$)$_3$ + O<u>H</u>].

Sharpless epoxidation of scalemic 3-methylcyclohex-2-en-1-ol (48): second step of double kinetic resolution.

To a stirred solution of *(R)*-3-methylcyclohex-2-en-1-ol (**48**) (69% ee) (0.275 g, 2.46 mmol), (-)-DiPT (0.087 g, 0.37 mmol), nonane (~ 0.1 mL) and molecular sieves (4Å) in CH_2Cl_2 (30 mL) at -23°C was added $Ti(OiPr)_4$ (0.07 mL, 0.24 mmol). An aliquot of the reaction mixture was removed and treated as described below so that the extent of the reaction could be monitored. After stirring for 2 h (catalyst conditioning), TBHP [0.7 mL (of a 3.6 M CH_2Cl_2 solution), 2.5 mmol] was added. After stirring for a further 5 h at -23°C, GLC (as described below) indicated that the reaction had proceeded to the desired 86% conversion. Standard non-acidic workup[45] was performed as follows: a solution of NaOH (30% w/v) in saturated brine (0.5 mL) and Et_2O (2 mL) were added and the reaction mixture was warmed to room temperature, then $MgSO_4$ (0.5 g) and celite (0.1 g) were added. Stirring for 15 min filtration and removal of solvent *in vacuo* yielded the crude product as a yellow oil. Flash chromatography was performed (silica, 2 : 1, Et_2O : petrol) and yielded recovered starting material [*(S)*-**48**] (0.028 g, 10%) {$[\alpha]_D^{22}$ = -36.5 (c = 0.9, $CHCl_3$)} and product [*(R,R,S,)*-**49**] (0.187 g, 59%) {$[\alpha]_D^{22}$ = +63.0 (c = 0.7, $CHCl_3$)} as colourless oils. Enantiomeric excesses were measured as described above, **48** was obtained with an enantiomeric excess of 38%, and **49** was obtained with an enantiomeric excess of 86%. ^{1}H NMR spectra of the recovered reactant (**48**) and the product (**49**) were identical to those described above.

Monitoring the extent of reaction of Sharpless epoxidations of 3-methyl-cyclohex-2-en-1-ol (48).

A freshly prepared aqueous solution of $FeSO_4$ (33% w/v) and tartaric acid (10% w/v) (~ 0.5 mL) was added to an aliquot (~ 0.5 mL) of the reaction mixture. The organic layer was separated, dried ($MgSO_4$) and filtered. The solution obtained was then injected onto a capillary GLC column (BP10, 25 m). A temperature gradient was used: (i) 3 min at 90°C (ii) 90 - 210°C at 15°min^{-1} (iii) 30 min at 210°C. Retention times for the various components of the reaction mixture were found to be as follows: nonane ~ 5 min, allylic alcohol (**48**) ~ 7.5 min, epoxide (**49**) ~ 8.5 min, DiPT ~ 13 min. The extent of reaction was calculated by observing the decrease in the ratio of starting material : internal standard (nonane).

Chapter 3

Experimental

Preparation of 1-(4-methoxyphenyl)ethanol (58)

4-Methoxyacetophenone (15.0 g, 0.10 mol) in Et_2O (100 mL) was added slowly to a mixture of $LiAlH_4$ (5.0 g, 0.13 mol) in Et_2O (200 mL) at 0°C under a nitrogen atmosphere. After stirring for 3 h at 0°C and then 3 h at room temperature, TLC indicated that all of the starting material had been consumed. The reaction mixture was cooled to 0°C and the excess $LiAlH_4$ was carefully quenched with 5 : 1 Et_2O/water (25 mL), 15% w/v NaOH solution (5 mL) and water (15 mL). The insoluble inorganic salts were removed by filtration through celite. Concentration of the filtrate *in vacuo* yielded the required product (**58**) (14.3 g, 94%).

58[145] : δ_H 7.32 [2H, d, J 8.6 Hz, Ph (*meta* to OMe)], 6.90 [2H, d, J 8.6 Hz, Ph (*ortho* to OMe)], 4.87 [1H, q, J 6.6 Hz, CHOH], 3.82 [3H, s, OCH_3], 1.82 [1H, br s, OH], 1.50 [3H, d, J 6.6 Hz, CH_3].

Preparation of 1-(4-methoxyphenyl)ethyl acetate (59)

To a stirred solution of **58** (2.00 g, 13.2 mmol), triethylamine (1.59 g, 15.6 mmol) and DMAP (5 mg) in CH_2Cl_2 (50 mL) was added acetic anhydride (1.46 g, 14.3 mmol). After stirring for 6 h at room temperature, TLC indicated that all of the starting material had been consumed. The reaction mixture was washed with saturated $NaHCO_3$ solution (30 mL) and after drying ($MgSO_4$), the organic layer was concentrated *in vacuo*. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave the required product (**59**) (2.23 g, 87%).

59[146] : δ_H 7.32 [2H, d, J 8.7 Hz, Ph (*meta* to OMe)], 6.90 [2H, d, J 8.7 Hz, Ph (*ortho* to OMe)], 5.85 [1H, q, J 6.6 Hz, CHOAc], 3.82 [3H, s, OCH_3], 2.07 [3H, s, $OCOCH_3$], 1.54 [3H, d, J 6.6 Hz, CH_3].

Measurement of the enantiomeric excesses of 58 and 59.

For the alcohol (**58**), preparation of Mosher's esters derivatives as described in the General Experimental followed by ^1H or ^{19}F NMR spectroscopy enabled enantiomeric

excess measurement. In the ^{1}H NMR spectrum of the Mosher's ester derivative of **58**, signals for the methoxy group were observed at ~ 3.55 ppm [*(S)*-**58**] and at ~ 3.47 ppm [*(R)*-**58**]. In the ^{19}F NMR spectrum, signals were observed at ~ -73.3 ppm [*(R)*-**58**] and at ~ -73.6 ppm [*(S)*-**58**]. Alternatively ^{1}H NMR spectroscopy of **58** in the presence of 1.5 equivalents of the chiral shift reagent *tris*-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [(+)-Eu(hfc)$_3$] gave rise to signals for the methyl group at ~ 9.4 ppm [*(S)*-**58**] and ~ 9.3 ppm [*(R)*-**58**].[147] The enantiomeric excess of the ester (**59**) was measured as described above after chemical hydrolysis (K_2CO_3/MeOH)

PFL mediated esterification of racemic 1-(4-methoxyphenyl)ethanol (58): first step of double kinetic resolution.

To a stirred solution of **58** (2.48 g, 16.3 mmol) and vinyl acetate (2.77 g, 32.2 mmol) in CH_2Cl_2 (30 mL) was added PFL (40 mg). The reactants were stirred at room temperature for 18 d, extent of reaction was monitored by ^{1}H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^{1}H NMR spectroscopy of the crude product indicated a conversion of 51%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**58**] (1.173 g, 47%) {$[\alpha]_D^{22}$ = -44.5 (c = 1.0, $CHCl_3$), literature [*(R)*-**58**: 85% ee][148]: $[\alpha]_D^{20}$ = +44.2 (c = 0.9 - 1.1, $CHCl_3$)} and the required product [*(R)*-**59**] (1.53 g, 48%) {$[\alpha]_D^{22}$ = +89.8 (c = 0.9, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **58** was obtained with an enantiomeric excess of 76%, and **59** was obtained with an enantiomeric excess of 74%. The product (**59**) and the recovered reactant (**58**) were used as starting materials in second kinetic resolutions as described below.

The lipase mediated esterification reactions shown in **Scheme 27** were performed in a similar manner.

PFL mediated hydrolysis of scalemic 1-(4-methoxyphenyl)ethyl acetate (59): second step of double kinetic resolution.

PFL (30 mg) was added to a stirred mixture of *(R)*-1-(4-methoxyphenyl)ethyl acetate (**59**) (74% ee) (0.50 g, 2.6 mmol) in pH 7 phosphate buffer (10 mL). As the reaction proceeded the pH was maintained by use of an autotitrator dispensing 1N NaOH solution. When 2.12 mL of NaOH solution had been added (corresponding to 82% conversion) the reaction was stopped by extraction with CH_2Cl_2 (10 x 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 82%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**59**] (0.060 g, 12%) {$[\alpha]_D^{22}$ = -32.7 (c = 1.0, $CHCl_3$)} and the required product [*(R)*-**58**] (0.302 g, 77%) {$[\alpha]_D^{22}$ = +58.6 (c = 1.0, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **59** was obtained with an enantiomeric excess of 27%, and **58** was obtained with an enantiomeric excess of >95%.

The lipase mediated hydrolysis reactions shown in **Scheme 28** were performed in a similar manner.

PFL mediated esterification of scalemic 1-(4-methoxyphenyl)ethanol (58): continuation of the first step of the double kinetic resolution.

To a stirred solution of *(S)*-**58** (76% ee) (0.50 g, 3.3 mmol) and vinyl acetate (0.57 g, 6.6 mmol) in CH_2Cl_2 (30 mL) was added PFL (50 mg). The reactants were stirred at room temperature for 26 d, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 20%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**58**] (0.348 g, 70%) {$[\alpha]_D^{22}$ = -55.7 (c = 1.2, $CHCl_3$)} and product [*(S)*-**59**] (0.093 g, 15%) {$[\alpha]_D^{22}$ = -8.5 (c = 1.2, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **58** was obtained with an enantiomeric excess of >95%, and **59** was obtained with an enantiomeric excess of 7%.

Chapter 4

Experimental

Preparation of 2-benzylpropan-1,3-diol (85), 2-(prop-2-ene)propan-1,3-diol (87) and 2-(1-methylnaphthyl)propan-1,3-diol (90).

Each diol was prepared by $LiAlH_4$ reduction of the corresponding 2-substituted diethyl malonate according to the literature procedure.[149]

85[58] : δ_H 7.25 [5H, m, Ph], 3.73 [4H, m, CH_2OH], 2.62 [2H, d, J 7.7 Hz, CH_2Ph], 2.43 [2H, br s, OH], 2.05 [1H, m, CH].

87[69] : δ_H 5.80 [1H, m, $CH=CH_2$], 5.07 [2H, m, $CH=CH_2$], 3.78, 3.64 [4H, ABX system, J_{AX} 4.1 Hz, J_{BX} 7.1 Hz, J_{AB} 10.8 Hz, CH_2OH], 2.91 [2H, br s, OH], 2.06 [2H, t, J 6.7 Hz, $CHCH_2CH=CH_2$], 1.87 [1H, m, $CHCH_2CH=CH_2$].

90[150] : δ_H 8.06-7.29 [7H, m, Np], 3.85, 3.75 [4H, ABX system, J_{AX} 3.5 Hz, J_{BX} 6.6 Hz, J_{AB} 10.6 Hz, CH_2OH], 3.09 [2H, d, J 7.4 Hz, CH_2Np], 2.42 [2H, br s, OH], 2.23 [1H, m, CH].

PFL mediated acetylation of 85 to give *(R)*-(+)-3-hydroxy-2-benzylpropyl acetate (86).

To a stirred solution of **85** (2.00 g, 12.0 mmol) and vinyl acetate (1.20 g, 14.0 mmol) in CH_2Cl_2 (50 mL) was added PFL (35 mg). The reactants were stirred for 8 d at room temperature, extent of reaction was monitored by TLC. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded the required product *(R)*-(+)-3-hydroxy-2-benzylpropyl acetate (**86**) (2.46 g, 98%) with >94% ee {calculated by comparison of specific rotation: $[\alpha]_D^{22}$ = +26.9 (c = 1.3, $CHCl_3$) with the literature value: +28.6 (c = 1.1, $CHCl_3$)[59a]} as a colourless oil.

86[58] : δ_H 7.27 [5H, m, Ph], 4.21, 4.09 [2H, ABX system, J_{AX} 4.7 Hz, J_{BX} 6.3 Hz, J_{AB} 11.2 Hz, CH_2OAc], 3.63, 3.52 [2H, ABX system, J_{AX} 4.7 Hz, J_{BX} 6.0 Hz, J_{AB} 11.3 Hz, CH_2OH], 2.72, 2.63 [2H, ABX system, J_{AX} 4.5 Hz, J_{BX} 4.0 Hz, J_{AB} 10.5 Hz, CH_2Ph], 2.13 [5H, m, CH + CH_3CO + OH].

The other enzyme catalysed reactions shown in **Scheme 41** were performed in a similar manner.

PFL mediated acetylation of 87 to give *(R)*-(+)-3-hydroxy-2-(prop-2-ene)propyl acetate (64).

To a stirred solution of **87** (3.89 g, 33.5 mmol) and vinyl acetate (4.30 g, 50.0 mmol) in CH_2Cl_2 (50 mL) was added PFL (60 mg). The reactants were stirred for 8 d at room temperature, extent of reaction was monitored by TLC. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. Flash chromatography of the crude product (silica, 2 : 1, Et_2O : petrol) yielded the diacetate (**87**) (0.40 g, 6%) {δ_H 5.75 [1H, m, C$\underline{H}$=CH_2], 5.08 [2H, m, CH=C$\underline{H_2}$], 4.11, 4.03 [4H, ABX system, J_{AX} 5.1 Hz, J_{BX} 6.1 Hz, J_{AB} 10.9 Hz, 2 x C$\underline{H_2}$OAc], 2.15 [3H, m, C$\underline{H}$C$\underline{H_2}$CH=CH_2], 2.07 [6H, s, 2 x C$\underline{H_3}$CO]} and *(R)*-(+)-3-hydroxy-2-(prop-2-ene)propyl acetate (**64**) (4.61 g, 88%) with 88% ee {calculated by comparison of specific rotation: $[\alpha]_D^{22}$ = +8.8 (c = 0.9, $CHCl_3$) with the literature value: +8.6 (86% ee) (c = 1.0, $CHCl_3$)[69]} as a colourless oil.

64[69] : δ_H 5.76 [1H, m, C$\underline{H}$=CH_2], 5.08 [2H, m, CH=C$\underline{H_2}$], 4.22, 4.10 [2H, ABX system, J_{AX} 4.8 Hz, J_{BX} 6.5 Hz, J_{AB} 11.3 Hz, C$\underline{H_2}$OAc], 3.61, 3.53 [2H, ABX system, J_{AX} 4.9 Hz, J_{BX} 6.7 Hz, J_{AB} 11.9 Hz, C$\underline{H_2}$OH], 2.14 [2H, m, C$\underline{H_2}$CH=CH_2], 2.07 [3H, s, C$\underline{H_3}$CO], 2.00 [2H, m, C$\underline{H}$ + O$\underline{H}$].

Protection of *(R)*-(+)-64 as its (*t*-butyl)dimethylsilyl ether.

To a stirred solution of *(R)*-(+)-**64** (1.63 g, 10.3 mmol) (88% ee) in CH_2Cl_2 (50 mL) was added (*i*-Pr)$_2$NEt (1.61 g, 12.4 mmol) and TBDMSCl (1.71 g, 11.4 mmol). The reactants were stirred at room temperature for 20 h and formed a dark red solution. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography (silica, 1 : 1, Et_2O : petrol) yielded recovered substrate (**64**) (0.43 g, 26%) and product *(S)*-(-)-3-[(*t*-butyl)dimethylsilyloxy]-2-(prop-2-ene)propyl acetate (**88**) (1.49 g, 72%) as a colourless oil.

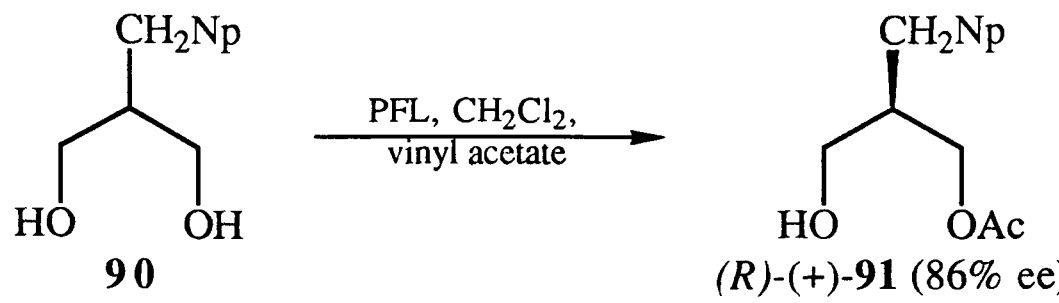
88 : Found : C, 61.5; H, 10.8. $C_{14}H_{28}O_3Si$ requires : C, 61.7; H, 10.4%; $[\alpha]_D^{22}$ = -1.0 (c = 1.0, $CHCl_3$) (88% ee); $\upsilon_{max.}$ 1730 (C=O), 1256, 839 (Si-C) cm^{-1}; δ_H 5.77 [1H, m, C<u>H</u>=CH_2], 5.05 [2H, m, CH=C<u>H</u>$_2$], 4.07 [2H, d, J 5.8 Hz, C<u>H</u>$_2$OAc], 3.59, 3.58 [2H, ABX system, J_{AX} 5.3 Hz, J_{BX} 5.8 Hz, J_{AB} 10.0 Hz, C<u>H</u>$_2$OSi], 2.21-1.84 [6H, m, C<u>H</u>C<u>H</u>$_2$CH=CH_2 + C<u>H</u>$_3$CO], 0.89 [9H, s, (C<u>H</u>$_3$)$_3$C], 0.04 [6H, s, Si(C<u>H</u>$_3$)$_2$]; δ_C 171.4 [<u>C</u>=O], 136.2 [<u>C</u>H=CH_2], 116.7 [CH=<u>C</u>H$_2$], 64.3 [<u>C</u>H$_2$OAc], 62.1 [<u>C</u>H$_2$OSi], 39.9 [<u>C</u>HCH$_2$CH=CH_2], 32.3 [<u>C</u>H$_2$CH=CH_2], 25.7 [SiC(<u>C</u>H$_3$)$_3$], 20.8 [<u>C</u>H$_3$CO], 18.1 [Si<u>C</u>(CH$_3$)$_3$], -5.8 [Si(<u>C</u>H$_3$)$_2$]; *m/z* 290 (M^++NH_4).

Protection of *(R)*-(+)-64 as its methoxymethyl ether.

To a stirred solution of *(R)*-(+)-**64** (0.99 g, 6.3 mmol) (88% ee) in CH_2Cl_2 (50 mL) was added (*i*-Pr)$_2$NEt (0.97 g, 7.5 mmol) and MOMCl (0.55 g, 6.8 mmol). The reactants were stirred at room temperature for 16 h. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and yielded recovered substrate (**64**) (0.17 g, 17%) and product *(R)*-(+)-3-(methoxymethyloxy)-2-(prop-2-ene)propyl acetate (**89**) (0.87 g, 69%) as a colourless oil.

89 : Found : C, 59.3; H, 9.3. $C_{10}H_{18}O_4$ requires : C, 59.4; H, 9.0%; $[\alpha]_D^{22}$ = +0.8 (c = 1.0, $CHCl_3$) (88% ee); $\upsilon_{max.}$ 1731 (C=O), 1046 (C-O) cm^{-1}; δ_H 5.79 [1H, m, C<u>H</u>=CH_2], 5.07 [2H, m, CH=C<u>H</u>$_2$], 4.61 [2H, s, OC<u>H</u>$_2$O], 4.10 [2H, d, J 5.7 Hz, C<u>H</u>$_2$OAc], 3.51 [2H, d, J 5.5 Hz, C<u>H</u>$_2$OMOM], 3.36 [3H, s, C<u>H</u>$_3$O] 2.21-2.00 [6H, m, C<u>H</u>C<u>H</u>$_2$CH=CH_2 + C<u>H</u>$_3$CO]; δ_C 171.3 [<u>C</u>=O], 135.8 [<u>C</u>H=CH_2], 117.1 [CH=<u>C</u>H$_2$], 96.6 [O<u>C</u>H$_2$O] 67.1 [<u>C</u>H$_2$OMOM], 64.3 [<u>C</u>H$_2$OAc], 55.1 [<u>C</u>H$_3$O] 37.9 [<u>C</u>HCH$_2$CH=CH_2], 32.7 [<u>C</u>H$_2$CH=CH_2], 20.7 [<u>C</u>H$_3$CO]; *m/z* 220 (M^++NH_4).

PFL mediated acetylation of 90 to give *(R)*-(+)-3-hydroxy-2-(1-methylnaphthyl)-propyl acetate (91) : first enantioselective reaction in two step process.

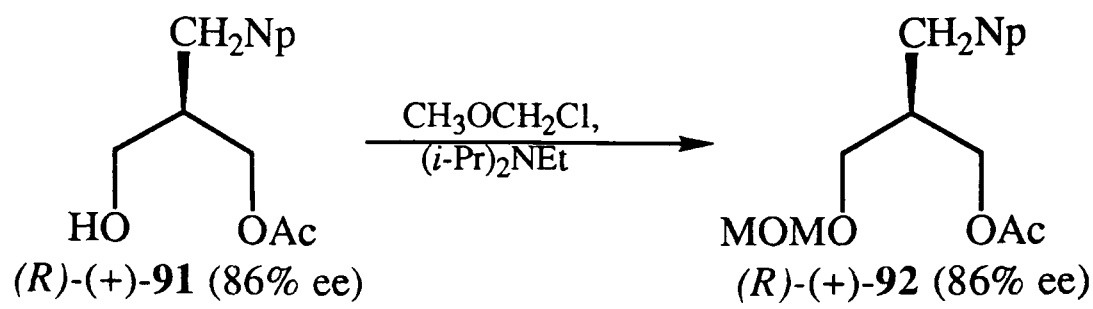


90 *(R)*-(+)-**91** (86% ee)

To a stirred solution of **90** (3.00 g, 13.9 mmol) and vinyl acetate (1.50 g, 17.4 mmol) in CH_2Cl_2 (50 mL) was added PFL (50 mg). The reactants were stirred for 14 d at room temperature, extent of reaction was monitored by TLC. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded the required product *(R)*-(+)-3-hydroxy-2-(1-methylnaphthyl)propyl acetate (**91**) (3.45 g, 96%) with 86% ee {calculated by comparison of specific rotation: $[\alpha]_D^{22}$ = +35.5 (c = 1.0, $CHCl_3$) with the literature value: +35.7 (86% ee) (c = 1.0, $CHCl_3$)[151]} as a colourless oil.

91[151] : Found : C, 74.3; H, 7.1. $C_{16}H_{18}O_3$ requires : C, 74.4; H, 7.0%; $\upsilon_{max.}$ 3300 (O-H), 1729 (C=O) cm^{-1}; δ_H 8.08-7.33 [7H, m, Np], 4.26, 4.17 [2H, ABX system, J_{AX} 4.9 Hz, J_{BX} 6.6 Hz, J_{AB} 11.6 Hz, CH_2OAc], 3.69, 3.60 [2H, ABX system, J_{AX} 4.7 Hz, J_{BX} 6.0 Hz, J_{AB} 11.3 Hz, CH_2OH], 3.20, 3.08 [2H, ABX system, J_{AX} 7.3 Hz, J_{BX} 7.4 Hz, J_{AB} 13.9 Hz, CH_2Np], 2.33 [1H, m, CH], 2.13 [3H, s, CH_3CO], 1.82 [1H, br s OH]; δ_C 172.0 [C=O], 135.7, 134.2, 132.1, [C1, C9, C10 : Np], 129.1, 127.5, 127.3, 126.2, 125.7, 125.5, 123.8 [C2-8 : Np], 64.2 [CH_2OAc], 62.2 [CH_2OH], 41.5 [CH], 31.3 [CH_2Np], 20.8 [CH_3CO]; *m/z* 276 (M^++NH_4).

Protection of *(R)*-(+)-91 as its methoxymethyl ether.



(R)-(+)-**91** (86% ee) *(R)*-(+)-**92** (86% ee)

To a stirred solution of *(R)*-(+)-**91** (0.42 g, 1.6 mmol) (86% ee) in CH_2Cl_2 (50 mL) was added $(i\text{-Pr})_2NEt$ (0.63 g, 4.8 mmol) and MOMCl (0.29 g, 3.6 mmol). The reactants were stirred at room temperature for 20 h. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded recovered substrate (**91**) (0.06 g, 15%) and product *(R)*-(+)-3-(methoxymethyloxy)-2-(1-methyl-naphthyl)propyl acetate (**92**) (0.41 g, 84%) with 86% ee [measured by HPLC (see below)] as a colourless oil.

92 : Found : C, 71.2; H, 7.4. $C_{18}H_{22}O_4$ requires : C, 71.5; H, 7.3%; $[\alpha]_D^{22}$ = +26.9 (c = 0.9, $CHCl_3$) (86% ee); $\upsilon_{max.}$ 1734 (C=O), 1045 (C-O) cm^{-1}; δ_H 8.11-7.31 [7H, m, Np], 4.65 [2H, s, $OC\underline{H}_2O$], 4.16 [2H, d, J 5.5 Hz, $C\underline{H}_2OAc$], 3.57 [2H, d, J 5.4 Hz, $C\underline{H}_2OMOM$], 3.39 [3H, s, $C\underline{H}_3O$] 3.26-3.12 [2H, ABX system, J_{AX} 7.4 Hz, J_{BX} 7.0 Hz, J_{AB} 14.1 Hz, $C\underline{H}_2Np$], 2.45 [1H, m, C<u>H</u>], 2.09 [3H, s $C\underline{H}_3CO$]; δ_C 171.3 [<u>C</u>=O], 135.8, 134.2, 132.1, [C1, C9, C10 : Np], 129.0, 127.5, 127.3, 126.1, 125.7, 125.5, 123.9 [C2-8 : Np], 96.8 [$O\underline{C}H_2O$], 67.3 [$\underline{C}H_2OMOM$], 64.6 [$\underline{C}H_2OAc$], 55.2 [$\underline{C}H_3O$], 39.3 [<u>C</u>H], 31.7 [$\underline{C}H_2Np$], 20.8 [$\underline{C}H_3CO$]; *m/z* 320 (M^++NH_4).

Measurement of enantiomeric excess of 92 and 94.

Enantiomeric excesses of **92** and **94** were measured by HPLC using a Chiralcel OB column (Jones). 1% Propan-2-ol in hexane was used as eluant at a flow rate of 0.5 $mLmin^{-1}$. Samples were dissolved in a portion of the eluant (1 $mgmL^{-1}$) and were injected on to the column *via* a Rheodyne valve using a 10 μL loop. Detection was by uv absorbance at 254 nm. Retention times for the two enantiomers of **92** were 44 min (*R*

enantiomer) and 64 min (*S* enantiomer). Enantiomeric excess measurement of **94** was performed by acetylation of the hydroxyl group with acetic anhydride (to give **92**) followed by HPLC as described above.

Preparation of 2-(1-methylnaphthyl)propan-1,3-diacetate (93).

To a stirred solution of **90** (0.53 g, 2.5 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (0.54 g, 5.3 mmol), DMAP (10 mg) and acetic anhydride (0.48 g, 4.7 mmol). After stirring for 14 h at room temperature, TLC indicated that all of the starting material had been consumed. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded monoacetylated product (**91**) (0.06 g, 9%) and 2-(1-methylnaphthyl)propan-1,3-diacetate (**93**) (0.67 g, 91%) as a colourless oil.

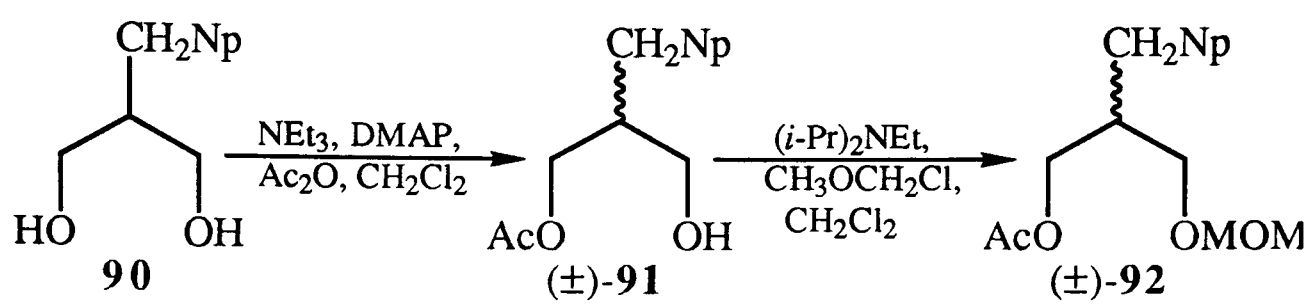
93[150] : δ_H 8.06-7.29 [7H, m, Np], 4.16, 4.09 [4H, ABX system, J_{AX} 5.4 Hz, J_{BX} 5.8 Hz, J_{AB} 11.3 Hz, 2 x CH_2OAc], 3.18 [2H, d, J 7.4 Hz, CH_2Np], 2.53 [1H, m, CH], 2.12 [6H, s, 2 x CH_3CO].

PFL mediated hydrolysis of 93 to give *(S)*-(-)-3-hydroxy-2-(1-methylnaphthyl)propyl acetate (91).

PFL (35 mg) was added to a stirred mixture of **93** (0.28 g, 0.9 mmol) in pH 7 phosphate buffer (10 mL). As the reaction proceeded the pH was maintained by use of an autotitrator dispensing 1N NaOH solution. When 0.48 mL of NaOH solution had been added (corresponding to 53% conversion) the reaction was stopped by extraction with CH_2Cl_2 (10 x 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed *in vacuo*. ^1H NMR spectroscopy of the crude product revealed a ratio of diacetate (**93**) : monoacetate (**91**) : diol (**90**) of 51 : 27 : 22. Flash chromatography (silica, 3 : 1, Et_2O : petrol) yielded recovered diacetate (**93**) (0.14 g, 50%), diol (**90**) (0.04 g, 20%) and *(S)*-(-)-monoacetate (**91**) (0.05 g, 21%) with 58% ee {calculated by comparison of specific rotation: $[\alpha]_D^{22}$ = -24.0 (c = 1.5, $CHCl_3$) with the literature value for *(R)*-(+)-**91**: +35.7 (86% ee) (c = 1.0, $CHCl_3$)[59a]}.

The other enzyme catalysed reactions in **Scheme 44** were performed in a similar manner.

Preparation of (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propyl acetate (92).



(±)-3-Hydroxy-2-(1-methylnaphthyl)propyl acetate (**91**) was prepared by treatment of 2-(1-methylnaphthyl)propan-1,3-diol (**90**) (2.03 g, 9.3 mmol) with triethylamine (1.12 g, 11.1 mmol), DMAP (10 mg) and acetic anhydride (1.03 g, 10.1 mmol) in CH_2Cl_2 (50 mL). Workup and flash chromatography were performed as in the preparation of **93** and yielded recovered starting material (**90**) (0.99 g, 49%), the diacetate (**93**) (0.18 g, 6%) and the required product (±)-**91** (0.87 g, 36%).

(±)-3-hydroxy-2-(1-methylnaphthyl)-propyl acetate (**91**) (0.65 g, 2.5 mmol) was then converted to (±)-**92** by treatment with (*i*-Pr)$_2$NEt (0.49 g, 3.8 mmol) and MOMCl (0.30 g, 3.7 mmol) in CH_2Cl_2 (50 mL). The reactants were stirred at room temperature for 24 h. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded recovered starting material (**91**) (0.14 g, 21%) and product (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propyl acetate (**92**) (0.54 g, 71%).

PFL mediated kinetic resolution of (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propyl acetate (92).

PFL (30 mg) was added to a stirred mixture of (±)-**92** (0.25 g, 0.8 mmol) in pH 7 phosphate buffer (10 mL). As the reaction proceeded the pH was maintained by use of an autotitrator dispensing 1N NaOH solution. When 0.31 mL of NaOH solution had been

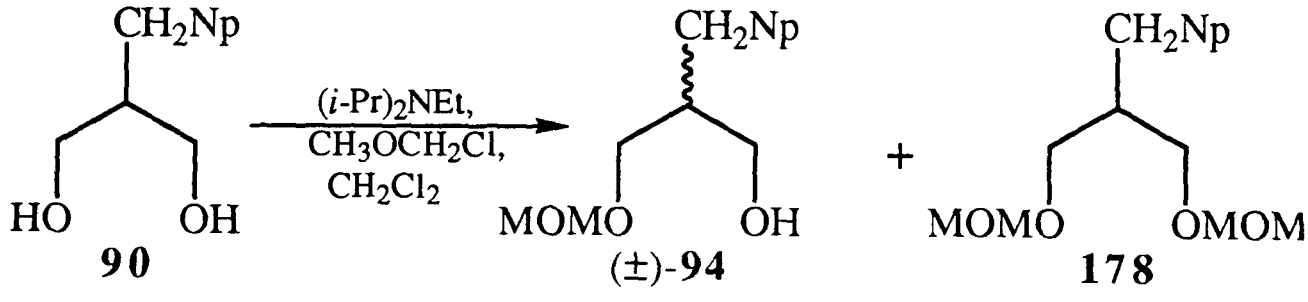
added (corresponding to 38% conversion) the reaction was stopped by extraction with CH_2Cl_2 (10 x 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed *in vacuo*. Flash chromatography (silica, 3 : 1, Et_2O : petrol) yielded recovered starting material *(S)*-(-)-**92** (0.12 g, 47%) {$[\alpha]_D^{22}$ = -8.3 (c = 1.9, $CHCl_3$)} and product *(S)*-(-)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (**94**) (0.06 g, 30%).

94[151] : Found : C, 73.9; H, 8.0. $C_{16}H_{20}O_3$ requires : C, 73.8; H, 7.7%; $[\alpha]_D^{22}$ = -13.2 (c = 1.2, $CHCl_3$) (55% ee) {literature (86% ee)[151]: $[\alpha]_D^{20}$ = -20.7 (c = 1.0, $CHCl_3$)}; $\upsilon_{max.}$ 3300 (O-H), 1045 (C-O) cm^{-1}; δ_H 8.08-7.33 [7H, m, Np], 4.65 [2H, s, OCH_2O], 3.73 [4H, m, CH_2OH + CH_2OMOM], 3.41 [3H, s, CH_3O] 3.16 [2H, d, J 7.4 Hz, CH_2Np], 2.31 [2H, m, CH + OH]; δ_C 136.2, 134.2, 132.1, [C1, C9, C10 : Np], 129.0, 127.4, 127.2, 126.0, 125.7, 125.5, 124.0 [C2-8 : Np], 96.9 [OCH_2O] 69.9 [CH_2OMOM], 64.7 [CH_2OH], 55.4 [CH_3O] 41.6 [CH], 31.4 [CH_2Np]; *m/z* 278 (M^++NH_4).

% Enantiomeric excesses of recovered starting material (**92**) and product (**94**) were measured by HPLC as described above and indicated: ee recovered starting material (**92**) = 32%, ee product (**94**) = 55%.

The other enzyme catalysed reactions described in **Scheme 45** were performed in a similar manner.

Preparation of (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (94).



To a stirred solution of **90** (0.63 g, 2.9 mmol) in CH_2Cl_2 (50 mL) was added (*i*-Pr)$_2$NEt (0.76 g, 5.8 mmol) and MOMCl (0.28 g, 3.5 mmol). The reactants were stirred at room temperature for 17 h. After washing with saturated $NaHCO_3$, the organic layer

was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded the required product (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (**94**) (0.33 g, 44%) and bis-1,3-(methoxymethyloxy)-2-(1-methylnaphthyl)propane (**178**) (0.22 g, 24%).

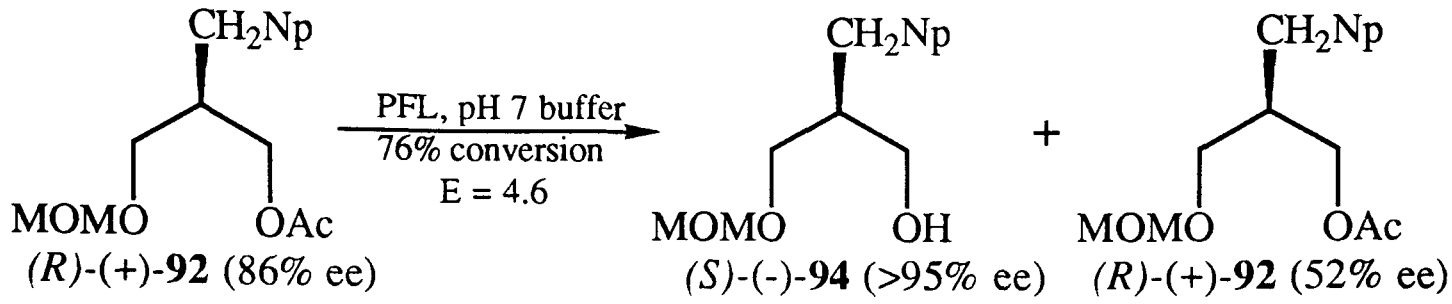
178 : Found : C, 71.2; H, 8.0. $C_{18}H_{24}O_4$ requires : C, 71.0; H, 8.0%; $\upsilon_{max.}$ 1041 (C-O) cm^{-1}; δ_H 8.16-7.33 [7H, m, Np], 4.65 [4H, s, 2 x OCH_2O], 3.59 [4H, d, J 5.6 Hz, 2 x CH_2OMOM], 3.39 [6H, s, 2 x CH_3O], 3.20 [2H, d, J 7.4 Hz, CH_2Np], 2.36 [1H, m, CH]; δ_C 136.5, 134.2, 132.3, [C1, C9, C10 : Np], 128.9, 127.5, 127.1, 126.0, 125.6, 125.5, 124.2 [C2-8 : Np], 96.9 [OCH_2O], 68.0 [CH_2OMOM], 55.2 [CH_3O], 40.4 [CH], 31.8 [CH_2Np]; *m/z* 304 (M^+).

PFL mediated acetylation of (±)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (94).

To a stirred solution of **94** (0.31 g, 1.2 mmol) and vinyl acetate (0.20 g, 2.3 mmol) in CH_2Cl_2 (50 mL) was added PFL (40 mg). The reactants were stirred for 36 d at room temperature, extent of reaction was monitored by TLC. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 33%. Flash chromatography was performed (silica, 3 : 1, Et_2O : petrol) and yielded recovered starting material *(R)*-(+)-**94** (0.18 g, 58%) {$[\alpha]_D^{22}$ = ~~+10.0~~ +3.3 (c = ~~1.0~~ 1.1, $CHCl_3$)}, and product *(R)*-(+)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propyl acetate (**92**) (0.12 g, 33%) {$[\alpha]_D^{22}$ = ~~+3.3~~ +10.0 (c = ~~1.1~~ 1.0, $CHCl_3$)}.

% Enantiomeric excesses of recovered starting material (**94**) and product (**92**) were measured by HPLC as described above and indicated: ee recovered starting material (**94**) = 14%, ee product (**92**) = 29%.

PFL mediated hydrolysis of *(R)*-(+)-92 (86% ee) : second enantioselective reaction in two step process.



PFL (35 mg) was added to a stirred mixture of *(R)*-(+)-**92** (0.20 g, 0.7 mmol) (86% ee) in pH 7 phosphate buffer (10 mL). As the reaction proceeded the pH was maintained by use of an autotitrator dispensing 1N NaOH solution. When 0.50 mL of NaOH solution had been added (corresponding to 76% conversion) the reaction was stopped by extraction with CH_2Cl_2 (10 x 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed *in vacuo*. Flash chromatography (silica, 3 : 1, Et_2O : petrol) yielded recovered starting material *(R)*-(+)-**92** (0.04 g, 20%) {$[\alpha]_D^{22}$ = +17.6 (c = 1.0, $CHCl_3$)}, and product *(S)*-(-)-3-(methoxymethyloxy)-2-(1-methylnaphthyl)propan-1-ol (**94**) (0.12 g, 68%) {$[\alpha]_D^{22}$ = -23.2 (c = 1.0, $CHCl_3$)}.

% Enantiomeric excesses of recovered starting material (**92**) and product (**94**) were measured by HPLC as described above and indicated: ee recovered starting material (**92**) = 52%, ee product (**94**) >95%.

Chapter 5

Experimental

Measurement of enantiomeric excesses of 96, 106 and 107.

Enantiomeric excesses of **96** were measured by preparation of Mosher's ester derivatives[46] (prepared as described in the General Experimental) followed by 500 MHz ^{1}H NMR spectroscopy. **106** and **107** were first hydrolysed (K_2CO_3, MeOH) to form **96** and then treated in a similar manner to that described above. In some experiments enantiomeric excesses were measured by comparison of the specific rotation of **96** with the literature value: $[\alpha]_D^{22} = +14.5$ (c = 0.7, EtOH).[73]

General procedure for the hydrolysis of 106 and 107.

The substrate (**106** or **107**) was added to a mixture of K_2CO_3 (1 g) and MeOH (10 mL). The reactants were stirred for 1 h at room temperature, after which the MeOH was removed *in vacuo*. Water (20 mL) was added to the residue and this was washed with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and after removal of the solvent *in vacuo* yielded **96**.

Preparation of trichloroethyl butyrate.

To a stirred solution of 2,2,2-trichloroethanol (5.01 g, 33.5 mmol) in CH_2Cl_2 (150 mL) was added triethylamine (4.12 g, 40.7 mmol), DMAP (25 mg) and butyryl chloride (3.89 g, 36.5 mmol). The reactants were stirred at room temperature for 48 h in a flask fitted with a reflux condenser. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Distillation of the crude product yielded trichloroethyl butyrate (5.82 g, 80%) as a colourless oil.

δ_H 4.76 [2H, s, C$\underline{H}_2$O], 2.46 [2H, t, J 7.4 Hz, C$\underline{H}_2$CO$_2$], 1.74 [2H, sx, J 7.4 Hz, CH$_3$C$\underline{H}_2$CH$_2$], 1.01 [3H, t, J 7.4 Hz, C$\underline{H}_3$].

Baker's yeast reduction of 6-methylhept-5-en-2-one (102) : first enantioselective reaction in two step process.[79]

To a stirred mixture of baker's yeast (Sigma) (100 g) in water (1 L) at 35 ^{o}C was added sucrose (Tate & Lyle) (72 g); fermentation ensued. After stirring for 1 h, distilled 6-

methylhept-5-en-2-one (5.00 g, 39.7 mmol) was added and stirring was continued. Sucrose (4 x 72 g) was added at 24 h intervals over the next 4 d. The reaction mixture was extracted with Et_2O (20 x 100 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography was performed (silica, 1 : 3, Et_2O : petrol) and gave recovered starting material (**102**) (0.75 g, 15%) and sulcatol (**96**) (3.35 g, 66%) with an enantiomeric excess of 85% (by ^1H NMR spectroscopy of the MTPA derivative).

96[73] : δ_H 5.12 [1H, m, C<u>H</u>=C], 3.79 [1H, sx, J 6.2 Hz, C<u>H</u>OH], 2.06 [3H, m, C<u>H</u>$_2$CHO<u>H</u>], 1.68, 1.62 [2 x 3H, 2 x s, (C<u>H</u>$_3$)$_2$C=C], 1.49 [2H, m, C<u>H</u>$_2$CH=C], 1.18 [3H, d, J 6.2 Hz, C<u>H</u>$_3$CHOH].

PFL mediated acetylation of *(RS)*-96 using vinyl acetate as acyl donor to give *(R)*-(-)-1,5-dimethylhex-4-enyl acetate (106) and *(S)*-(+)-96.

To a stirred solution of *(RS)*-**96** (0.25 g, 2.0 mmol) and vinyl acetate (0.25 g, 2.9 mmol) in CH_2Cl_2 (10 mL) was added PFL (30 mg). The reactants were stirred for 8 d at room temperature, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 45%. Flash chromatography was performed (silica, 1 : 2, Et_2O : petrol) and yielded recovered starting material *(S)*-(+)-**96** (0.12 g, 48%) with 39% ee {calculated by comparison of specific rotation : $[\alpha]_D^{22}$ = +5.7 (c = 1.1, EtOH) with the literature value: +14.5 (c = 0.7, EtOH)[73]}, and product *(R)*-(-)-1,5-dimethylhex-4-enyl acetate (**106**) (0.11 g, 33%) with 47% ee {calculated by comparison of the specific rotation of the hydrolysis product (**96**): $[\alpha]_D^{22}$ = -6.8 (c = 1.0, EtOH) with the literature value[73]}.

106[84] : $[\alpha]_D^{22}$ = -5.2 (c = 0.9, EtOH) (47% ee); δ_H 5.07 [1H, m, C<u>H</u>=C], 4.88 [1H, sx, J 6.3 Hz, C<u>H</u>OAc], 2.00 [5H, m, C<u>H</u>$_2$CHOCOC<u>H</u>$_3$], 1.72-1.42 [8H, m, (C<u>H</u>$_3$)$_2$C=CHC<u>H</u>$_2$], 1.20 [3H, d, J 6.3 Hz, C<u>H</u>$_3$CHOAc].

The other enzyme catalysed reactions, using vinyl acetate as acyl donor, shown in **Scheme 55** were performed in a similar manner.

PFL mediated acylation of *(RS)*-96 using trichloroethyl butyrate as acyl donor to give *(R)*-(-)-1,5-dimethylhex-4-enyl butanoate (107) and *(S)*-(+)-96.

To a stirred solution of *(RS)*-**96** (1.02 g, 8.0 mmol) and trichloroethyl butyrate (1.92 g, 8.8 mmol) in CH_2Cl_2 (50 mL) was added PFL (75 mg). The reactants were stirred for 14 d at room temperature, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 48%. Flash chromatography was performed (silica, 1 : 3, Et_2O : petrol) and gave fractions containing recovered starting material *(S)*-(+)-**96** (0.49 g, 48%) with 46% ee (measured by ^1H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = +6.4 (c = 1.0, EtOH)}, and a mixture of trichlororethyl butyrate and *(R)*-1,5-dimethylhex-4-enyl butyrate (**107**). Hydrolysis of the mixture of butyrates, as described above, yielded *(R)*-(-)-**96** (0.43 g, 42%) with 50% ee (measured by ^1H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = -7.4 (c = 1.0, EtOH)}.

The other enzyme catalysed reactions, using trichloroethyl butyrate as acyl donor, shown in **Scheme 55** were performed in a similar manner.

CCL mediated acylation of *(S)*-(+) 96 (85% ee) : second enantioselective reaction in two step process.

To a stirred solution of *(S)*-(+)-**96** (85% ee) (0.49 g, 3.8 mmol) and trichloroethyl butyrate (0.92 g, 4.2 mmol) in CH_2Cl_2 (50 mL) was added CCL (1.02 g). The reactants were stirred for 5 d at room temperature, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 81%. Flash chromatography was performed (silica, 1 : 3, Et_2O : petrol) and gave fractions containing recovered starting material *(S)*-(+)-**96** (0.06 g, 12%) with 41% ee (measured by ^1H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = +5.4 (c = 1.0, EtOH)}, and a mixture of trichlororethyl butyrate and *(S)*-1,5-dimethylhex-4-enyl butyrate

(**107**). Hydrolysis of the mixture of butyrates, as described above, yielded *(S)*-(+)-**96** (0.34 g, 69% over two steps) with >95% ee (measured by ^{1}H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = +14.2 (c = 1.2, EtOH)}.

PFL mediated acylation of *(S)*-(+) 96 (85% ee) : alternative second enantioselective reaction in two step process.

To a stirred solution of *(S)*-(+)-**96** (85% ee) (0.51 g, 4.0 mmol) and trichloroethyl butyrate (0.94 g, 4.3 mmol) in CH_2Cl_2 (50 mL) was added PFL (100 mg). The reactants were stirred for 8 d at room temperature, extent of reaction was monitored by ^{1}H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent *in vacuo*. ^{1}H NMR spectroscopy of the crude product indicated a conversion of 33%. Flash chromatography was performed (silica, 1 : 3, Et_2O : petrol) and gave fractions containing recovered starting material *(S)*-(+)-**96** (0.30 g, 59%) with >95% ee (measured by ^{1}H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = +14.1 (c = 1.0, EtOH)}, and a mixture of trichlororethyl butyrate and *(S)*-1,5-dimethylhex-4-enyl butyrate (**107**). Hydrolysis of the mixture of butyrates, as described above, yielded *(S)*-(+)-**96** (0.12 g, 24% over two steps) with 65% ee (measured by ^{1}H NMR spectroscopy of the MTPA derivative) {$[\alpha]_D^{22}$ = +9.9 (c = 1.1, EtOH)}.

Chapter 6

Experimental

Preparation of *(RS)*-(α-methylbenzyl)benzyl amine (143).

Benzaldehyde (10.0 g, 94.3 mmol) and *(RS)*-α-methylbenzylamine (10.0 g, 82.5 mmol) were refluxed for 4 h in EtOH (250 mL). The reaction mixture was cooled to 0°C with an ice bath and sodium borohydride (1.6 g, 42.3 mmol) was added. After stirring for 16 h at room temperature the solvent was removed *in vacuo*. The remaining slurry was dissolved in water (200 mL), extracted with CH_2Cl_2 (3 x 100 mL) and dried ($MgSO_4$). After filtration and concentration, *(RS)*-**143** (15.5 g, 89%) was obtained as a pale yellow oil. The amine was purified by flash chromatography (silica, 1 : 1, Et_2O : petrol) as and when required.

143[152] : δ_H 7.32 [10H, m, 2 x Ph], 3.84 [1H, q, J 6.6 Hz, CH], 3.68, 3.62 [2H, AB system, J_{AB} 17.9 Hz, CH_2Ph], 1.71 [1H, br s, NH], 1.40 [3H, d, J 6.6 Hz, CH_3].

(R) and *(S)*-**143** were prepared by the same method using *(R)* and *(S)*-α-methylbenzylamine.

Preparation of N,N-dimethyl cinnamide (141).

To a stirred solution of distilled cinnamoyl chloride (5.0 g, 29.9 mmol) and dimethylamine.HCl salt (2.7 g, 33.1 mmol) in CH_2Cl_2 (100 mL) at 0°C was added pyridine (5.2 g, 65.7 mmol). After stirring at room temperature for 1 h, the solvent was removed *in vacuo*, and saturated brine (50 mL) was added to the residue. Extraction with CH_2Cl_2 (3 x 100 mL) followed by drying ($MgSO_4$), filtration and concentration yielded a brown solid. Recrystallisation (hexane/CH_2Cl_2) gave the required product (**141**) as a white solid (4.80 g, 92%). mp 91 - 94°C (lit: 96 - 98°C)

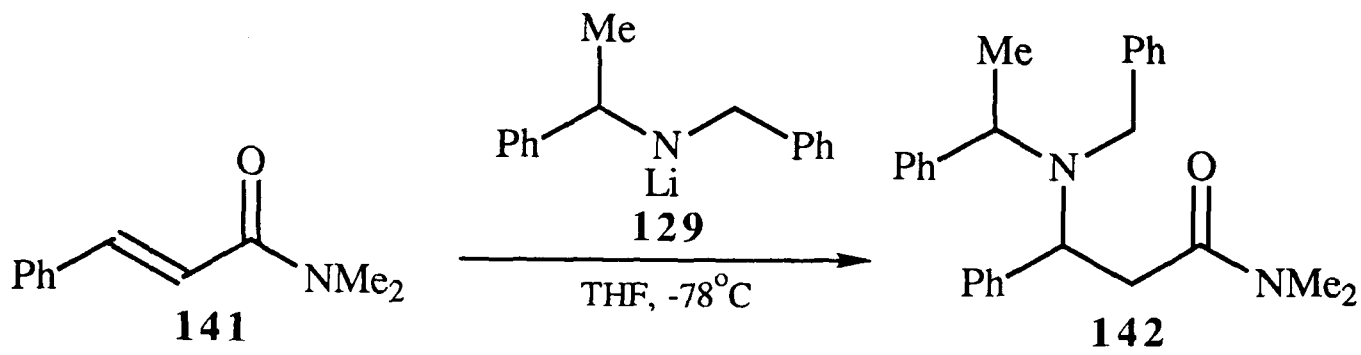
141[153] : δ_H 7.67 [1H, d, J 15.6 Hz, PhCH], 7.43 [5H, m, Ph], 6.89 [1H, d, J 15.6 Hz, $CHCONMe_2$], 3.17, 3.06 [6H, 2 x s, $N(CH_3)_2$].

Measurement of enantiomeric excess of 143.[121]

The sample of **143** (10 mg, 0.05 mmol) of interest and *(R)*-O-acetyl mandelic acid (**144**) (10 mg, 0.05 mmol) were mixed together in an NMR tube with $CDCl_3$. ^1H NMR spectroscopy (200 MHz) enabled measurement of the diastereomeric excess of the resulting

salt *via* integration of the α-methylbenzyl doublets at 1.0 - 1.3 ppm. The value obtained corresponds to the enantiomeric excess of the sample of **143**.

Michael addition reaction of lithium[*(RS)*-α-methylbenzyl]benzyl amide (129) and N,N-dimethyl cinnamide (141) to give *(SR)*-N,N-dimethyl-3-phenyl-3-(N-benzyl, N-*(RS)*-α-methylbenzyl)aminopropanamide (142).



Butyllithium (1.7 mL, 2.7 mmol) was added to a stirred solution of *(RS)*-(α-methylbenzyl)benzyl amine (**143**) (0.63 g, 2.9 mmol) in THF (25 mL) at 0°C, resulting in the formation of a pink-red solution of the lithium amide *(RS)*-(**129**). After stirring at 0°C for 30 min and then for 1 h at -78°C, N,N-dimethyl cinnamide (**141**) (0.30 g, 1.7 mmol) in THF (5 mL) was added dropwise and stirring was continued for 1 h at -78°C. MeOH (1 mL) was added and the reaction mixture was warmed to room temperature. Removal of solvent *in vacuo*, addition of CH_2Cl_2 (30 mL) and filtration through alumina (10% deactivated) yielded (after removal of the solvent *in vacuo*) the crude product as a yellow oil. Flash chromatography (silica, 1 : 1, Et_2O : petrol) allowed recovery of the amine (**143**) (0.29 g) and the Michael adduct *(SR)*-N,N-dimethyl-3-phenyl-3-(N-benzyl, N-*(RS)*-α-methylbenzyl)aminopropanamide (**142**) (0.60 g, 91%) with >94% diastereomeric excess[154] both as colourless oils.

(SR,RS)-**142*** : Found : C, 80.8; H, 7.7; N, 7.1. $C_{26}H_{30}N_2O$ requires : C, 80.8; H, 7.8; N, 7.2%; $\upsilon_{max.}$ 1633 (C=O) cm^{-1}; δ_H 7.34 [15H, m, Ph], 4.62 [1H, t, J 6.8 Hz, PhC<u>H</u>(CH_2)N], 4.03 [1H, q, J 6.7 Hz, PhC<u>H</u>(CH_3)N], 3.83, 3.72 [2H, AB system, J_{AB} 14.9 Hz, C<u>H</u>$_2$Ph], 2.78 [3H, s, NC<u>H</u>$_3$], 2.51 [2H, d, J 6.8 Hz, C<u>H</u>$_2$CO], 2.43 [3H, s, NC<u>H</u>$_3$], 1.36 [3H, d, J 6.7 Hz, PhCHC<u>H</u>$_3$]; δ_C 171.2 [<u>C</u>=O], 144.4, 143.7, 142.6,

128.5, 128.1, 127.2, 127.0, 126.8, 126.6 [Ph], 60.3 [PhCH(CH_2)N], 56.5 [PhCH(CH_3)N], 50.6 [PhCH_2], 37.8 [CH_2CO], 36.7 [NCH_3], 35.2 [NCH_3], 13.5 [CHCH_3]; *m/z* 387 (M^++1).

*See below for the specific rotation of homochiral *(R,S)*-**142**.

Measurement of enantiomeric excess of 142.

The sample of **142** (18 mg, 0.05 mmol) of interest and *(R)*-O-acetyl mandelic acid (**144**) (10 mg, 0.05 mmol) were mixed together in an NMR tube with C_6D_6. ^{1}H NMR spectroscopy (500 MHz) enabled measurement of the diastereomeric excess of the resulting salt *via* integration of the α-methylbenzyl doublets at 1.0 - 1.3 ppm. The value obtained corresponds to the enantiomeric excess of the sample of **142**.

Experiments performed to determine the stoicheiometry of the reaction between homochiral or racemic 129 and 141.

The experiments shown in **Table 6** were performed as described above using the indicated amounts of homochiral or racemic **129**. In each case, the conversion was measured by ^{1}H NMR spectroscopy of the crude product.

Experiments performed to test for the existence of a nonlinear effect in the reaction of 129 and 141.

The experiments shown in **Table 7** were performed as described above using 1.6 equivalents of lithium amide (**129**) of the required enantiomeric excess. Enantiomeric excesses of the starting material (**143**), the Michael adduct (**142**) and the recovered starting material (**143**) were measured using the previously described methods.

In the reaction using homochiral **143** (Entry 5), *(S)*-**143** was used. The product obtained was *(R)*-N,N-dimethyl-3-phenyl-3-(N-benzyl, N-*(S)*-α-methylbenzyl)aminopropanamide (**142**) with a specific rotation of $[\alpha]_D^{22}$ = -10.6 (c = 0.9, CH_2Cl_2).

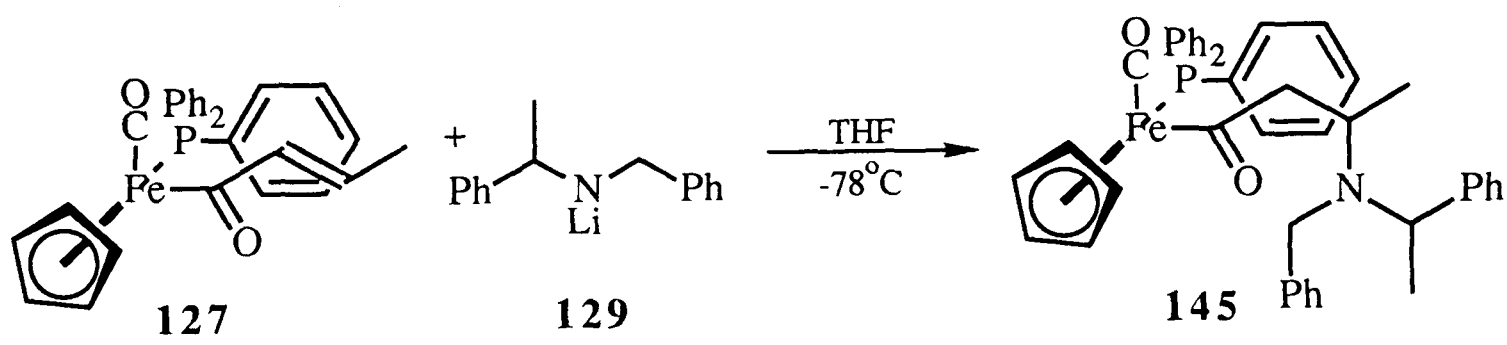
Preparation of the iron crotonyl complex E-[(η^5-C_5H_5)Fe(CO)(PPh_3)-($COCH{=}CHCH_3$)] (127).

(RS)-Iron crotonyl complex (**127**) was prepared *via* the sodium hydride mediated elimination of MeOH from the O-methylated acetaldehyde aldol product of *(RS)*-(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**) as described in reference 138. An overall yield of 84% was obtained from *(RS)*-(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_3$) (**15**).

127[138] : δ_H 7.43 [15H, m, P<u>Ph</u>$_3$], 6.51 [1H, d, J 15.1 Hz, COC<u>H</u>], 5.54 [1H, dq, J 15.1, 6.8 Hz, C<u>H</u>CH_3], 4.44 [5H, d, J_{PH} 1.2 Hz, C_5<u>H</u>$_5$], 1.58 [3H, d, J 6.8 Hz, C<u>H</u>$_3$].

(R)-**127** was prepared as described above using *(R)*-(η^5-C_5H_5)Fe(CO)(PPh_3)-($COCH_3$) (**15**).

Michael addition reaction of lithium-[*(RS)*-α-methylbenzyl]benzyl amide (129) and iron crotonyl complex *(RS)*-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)-($COCH{=}CHCH_3$)] (127) to give the Michael adduct (145).



127 **129** **145**

Butyllithium (0.5 mL, 0.80 mmol) was added to a stirred solution of *(RS)*-(α-methylbenzyl)benzyl amine (**143**) (0.18 g, 0.84 mmol) in THF (25 mL) at 0°C, resulting in the formation of a pink-red solution of the lithium amide *(RS)*-(**129**). After stirring at 0°C for 30 min and then for 1 h at -78°C, *(RS)*-iron crotonyl complex (**127**) (0.20 g, 0.42 mmol) in THF (10 mL) at -78°C was added by cannula and stirring was continued for 1 h at -78°C. MeOH (1 mL) was added and the reaction mixture was warmed to room temperature. Removal of solvent *in vacuo*, addition of CH_2Cl_2 (30 mL) and filtration through alumina (10% deactivated) yielded (after removal of the solvent *in vacuo*) the crude

product as an orange oil. Flash chromatography (silica, 1 : 4, Et_2O : petrol) yielded recovered amine (**143**) (0.04 g) as a colourless oil, and the Michael adduct (**145**)† (0.19 g, 67%) as a yellow solid with a diastereomeric ratio of 96 : 2 : 2* [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*].[155]

†See below for characterisation of *(R,R,R)*, *(R,R,S)*, and *(R,S,S)*-**145**.

*Identical to the diastereomeric ratio of the crude product.

Experiments performed to determine the stoicheiometry of the reaction between 129 and 127.

The experiments shown in **Tables 8** to **12** were performed as described above using the indicated amounts of homochiral or racemic **127** and **129**. Experiments using racemic **129** and those between the mismatched pair were left stirring at -78°C for up to 6 h. However the conversions observed were no greater than those observed when shorter reaction periods were used. In each case, the conversion and diastereomeric excess were measured by ^1H NMR spectroscopy of the crude product.

In the reaction between the matched pair [*(R)*-**129** and *(R)*-**127**], the product obtained was *(R,R,R)*-**145**, no trace of the *(R,S,R)* diastereomer was seen.

(R,R,R)-**145** : Found : C, 75.0; H, 6.0; N, 1.9. $C_{43}H_{42}FeNO_2P$ requires : C, 74.7; H, 6.1; N, 2.0%; $[\alpha]_D^{22}$ = -43.2 (c = 0.04, benzene); $\upsilon_{max.}$ 1913 vs (CO), 1601 s (CO) cm^{-1}; δ_H 7.34 [25H, m, 2 x Ph + PPh_3], 4.22 [5H, d, J_{PH} 0.8 Hz, C_5H_5], 3.80 [1H, q, J 6.8 Hz, PhCH], 3.66, 3.58 [2H, AB system, J_{AB} 15.1 Hz, CH_2Ph], 3.20 [1H, m, $COCH_2CH$], 2.93 [1H, d, J 16.2 Hz, CHHCO], 2.48 [1H, dd, J 16.2, 10.5 Hz, CHHCO], 1.26 [3H, d, J 6.9 Hz, $PhCH(N)CH_3$], 0.52 [3H, d, J 6.6 Hz, $CH_2CH(N)CH_3$]; δ_C 276.2, 221.3 [2 x CO], 145.0, 143.0, 137.1, 136.3, 133.5, 133.3, 129.8, 128.3, 128.1, 127.9, 127.8, 126.6, 126.4 [Ph + PPh_3], 85.1 [C_5H_5], 71.1 [CH_2CO], 58.1 [CHPh], 50.3 [CH_2Ph], 48.0 [$COCH_2CH$], 19.2, 19.1 [2 x CH_3]; δ_P 72.46 [PPh_3]; *m/z* 692 (M^++1).

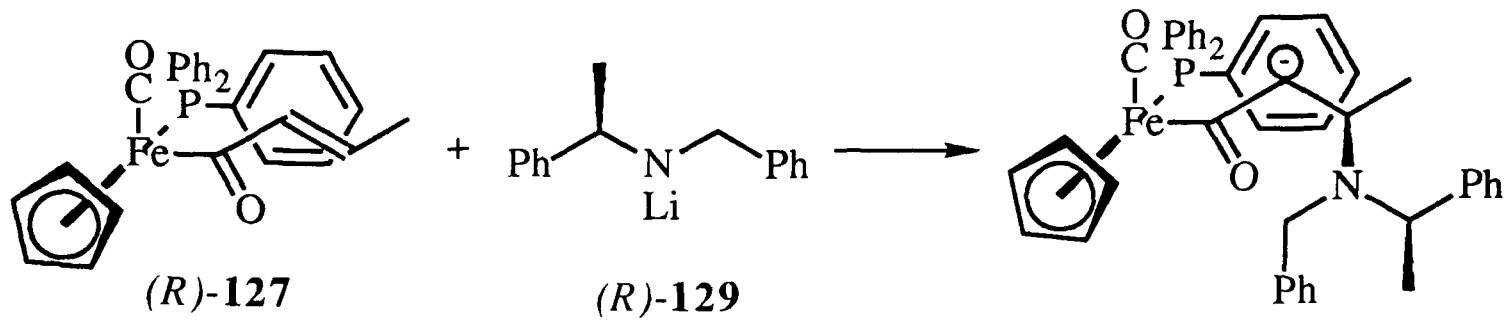
In the reaction between the mismatched pair [*(S)*-**129** and *(R)*-**127**], the product obtained was a 1 : 1 mixture of *(R,R,S)* : *(R,S,S)*-**145**. Recrystallisation (petrol/CH_2Cl_2) enabled separation of the two diastereomers.

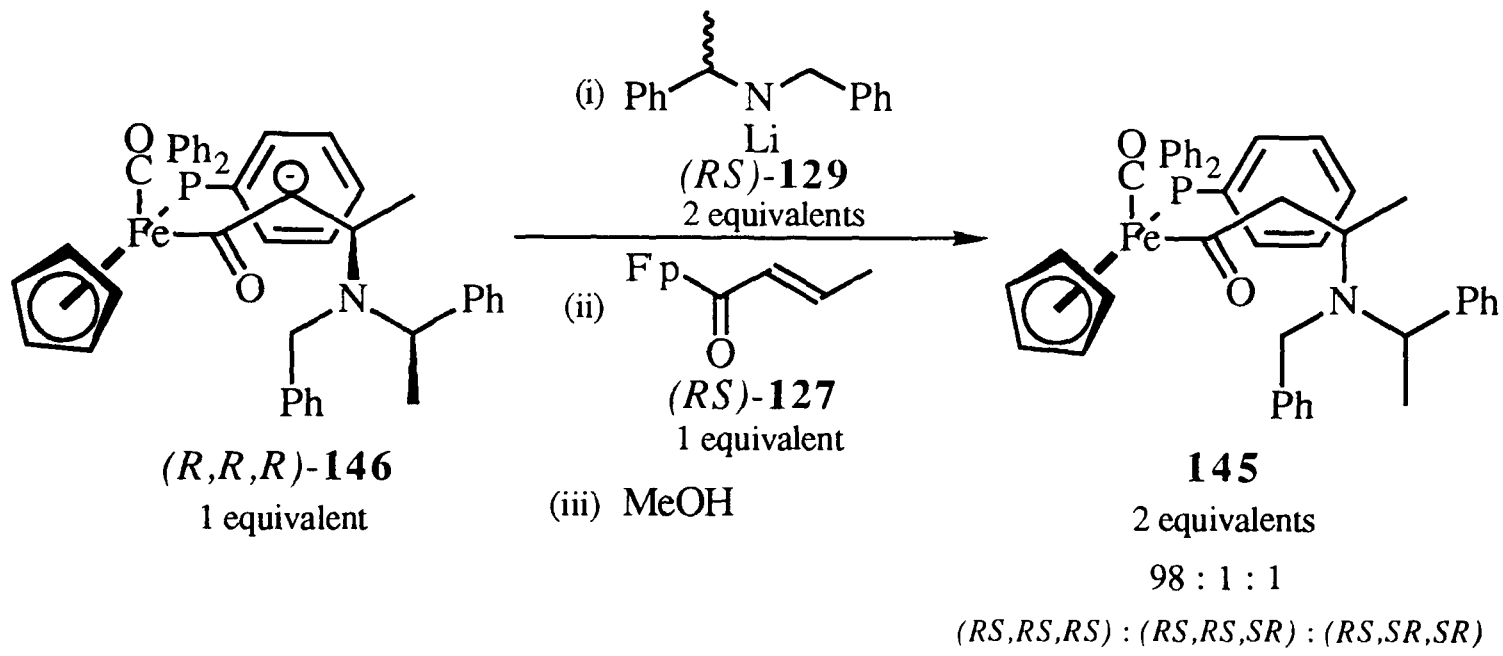
145 (less soluble in petrol/CH_2Cl_2 of *RRS* and *RSS*) : Found : C, 74.5; H, 6.2; N, 1.9. $C_{43}H_{42}FeNO_2P$ requires : C, 74.7; H, 6.1; N, 2.0%; δ_H 7.30 [25H, m, 2 x Ph + PPh_3], 4.29 [5H, s, C_5H_5], 3.84 [1H, q, J 6.8 Hz, PhCH], 3.67, 3.57 [2H, AB system, J_{AB} 15.4 Hz, CH_2Ph], 3.33 - 3.19 [2H, m, $COCH_2CH$ + $CHHCO$], 2.40 [1H, dd, J 14.8, 10.0 Hz, $CHHCO$], 1.28 [3H, d, J 6.7 Hz, $PhCH(N)CH_3$], 0.49 [3H, d, J 6.3 Hz, $CH_2CH(N)CH_3$]; δ_C 275.7, 220.5 [2 x CO], 145.6, 142.9, 136.7, 136.3, 133.4, 133.3, 129.6, 128.4, 128.0, 127.7, 127.6, 126.3, 126.2 [Ph + PPh_3], 85.2 [C_5H_5], 72.3 [CH_2CO], 58.2 [CHPh], 50.2 [CH_2Ph], 48.7 [$COCH_2CH$], 19.1, 16.8 [2 x CH_3]; δ_P 72.15 [PPh_3]; *m/z* 692 (M^++1).

145 (more soluble in petrol/CH_2Cl_2 of *R,R,S* and *R,S,S*) : selected δ_H 4.32 [5H, d, J_{PH} 0.8 Hz, C_5H_5], 1.16 [3H, d, J 6.7 Hz, $PhCH(N)CH_3$], 0.94 [3H, d, J 6.2 Hz, $CH_2CH(N)CH_3$]; δ_P 73.06 [PPh_3].

Experiments performed to test for the occurrence of selective chelation :

1 : Addition of two equivalents of *(RS)*-129 followed by one equivalent of *(RS)*-127 to the enolate *(R,R,R)*-146.

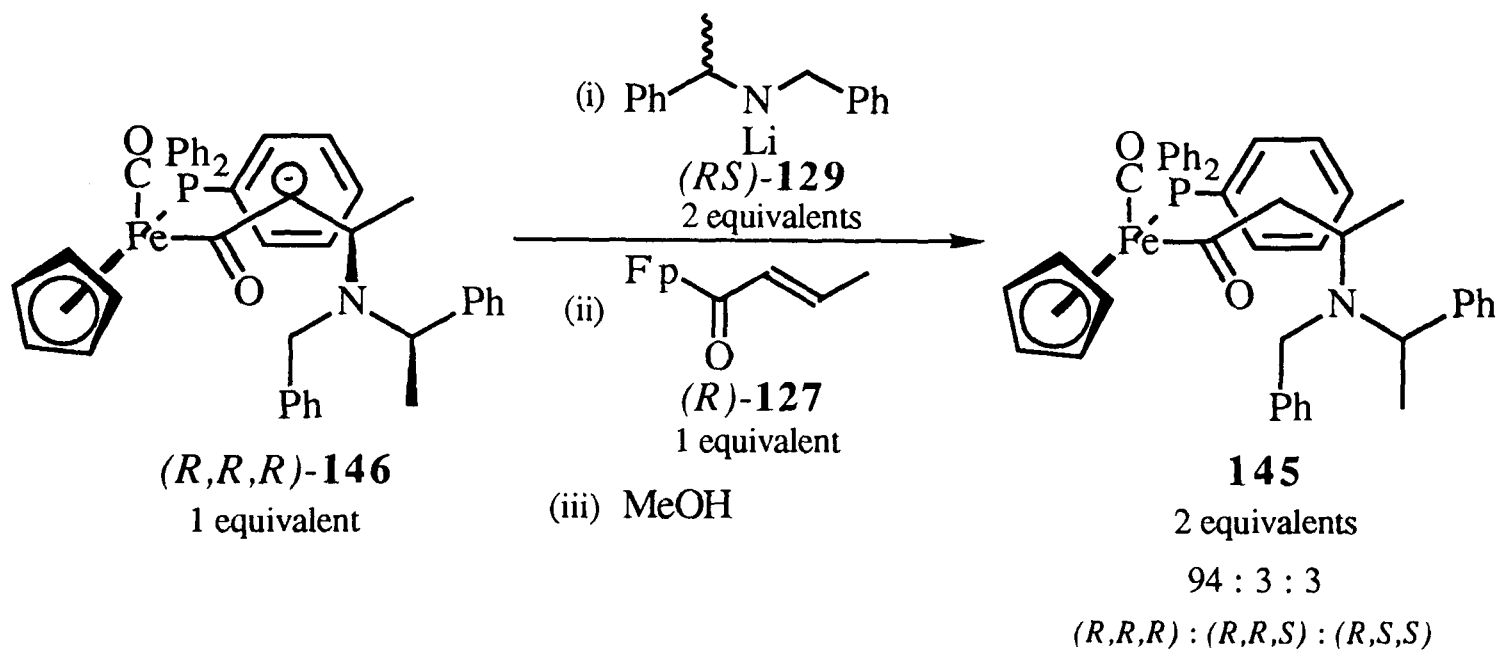




Butyllithium (0.1 mL, 0.16 mmol) was added to a stirred solution of *(R)*-(α-methylbenzyl)benzyl amine (**143**) (0.038 g, 0.18 mmol) in THF (15 mL) at 0°C, resulting in the formation of a pink-red solution of the lithium amide *(R)*-(**129**). After stirring at 0°C for 30 min and then for 1 h at -78°C, *(R)*-iron crotonyl complex (**127**) (0.077 g, 0.16 mmol) in THF (10 mL) at -78°C was added by cannula, resulting in the formation of a dark orange solution (**637**), and stirring was continued for 3 h at -78°C. A solution of *(RS)*-**129** was prepared [by the addition of butyllithium (0.2 mL, 0.32 mmol) to a solution of *(RS)*-**143** (0.078 g, 0.37 mmol) in THF (15 mL) at 0°C and stirring for 30 min at 0°C and then for 1 h at -78°C] and added by cannula to the reaction mixture. The reactants were stirred together at -40°C for 2 h and then cooled to -78°C. *(RS)*-Iron crotonyl complex (**127**) (0.078 g, 0.16 mmol) in THF (10 mL) was added by cannula at -78°C and the dark

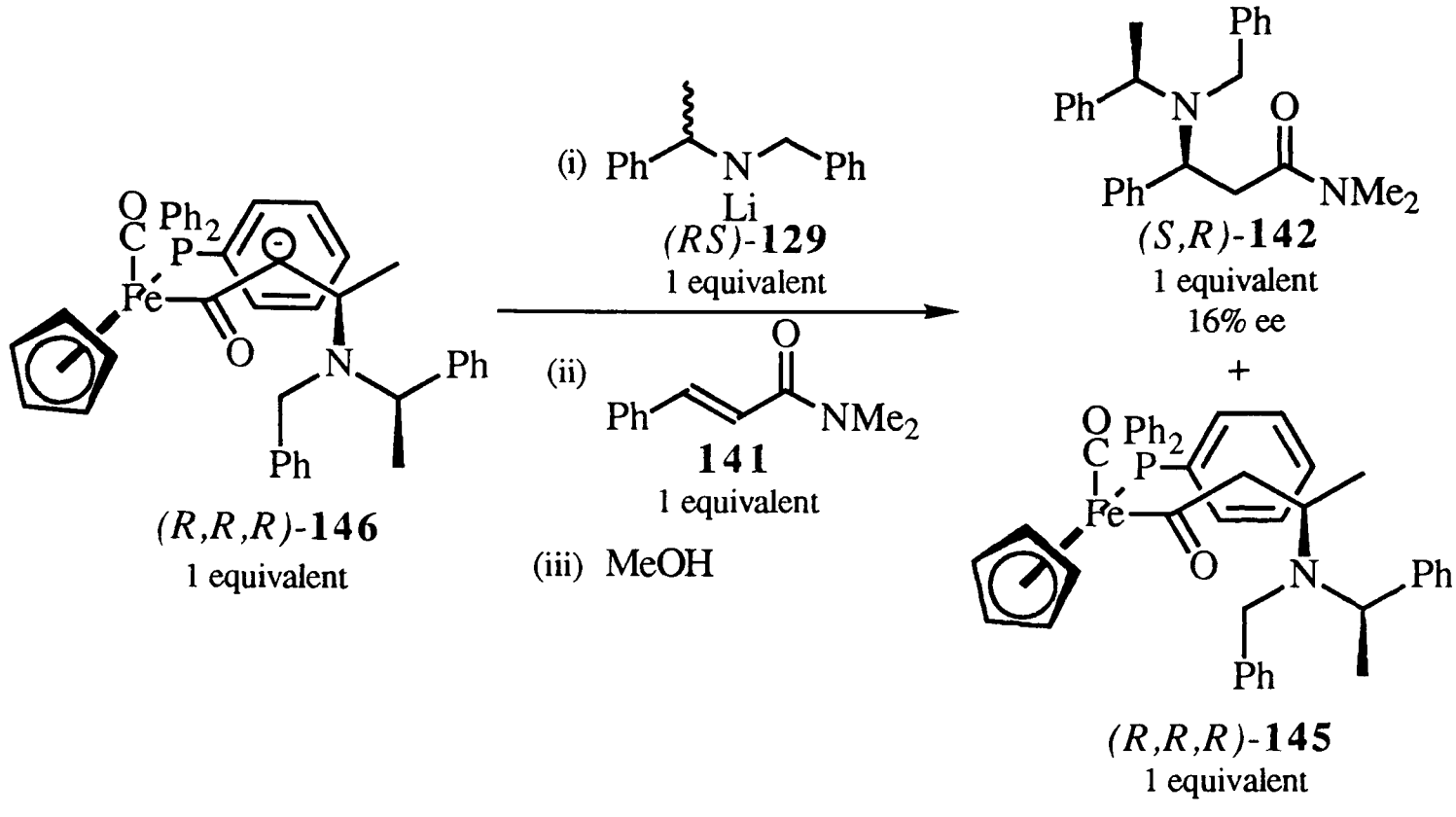
orange solution obtained was stirred for a further 3 h after which MeOH (1 mL) was added and the reaction mixture was warmed to room temperature. Removal of solvent *in vacuo*, addition of CH_2Cl_2 (30 mL) and filtration through alumina (10% deactivated) yielded (after removal of the solvent *in vacuo*) the crude product as an orange oil. ^1H NMR spectroscopy (500 MHz) of the crude product revealed that complete conversion of **127** to the Michael adduct (**145**) had occurred. The diastereomeric ratio of the product was found to be 98 : 1 : 1 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*].

2 : Addition of two equivalents of *(RS)*-129 followed by one equivalent of *(R)*-127 to the enolate *(R,R,R)*-146.



The second experiment to test for selective chelation was performed as descibed above except that instead of adding *(RS)*-**129**, *(R)*-**129** was added. Once again ^1H NMR spectroscopy (500 MHz) of the crude product revealed that complete conversion of **127** to the Michael adduct (**145**) had occurred. In this case the diastereomeric ratio of the product was found to be 94 : 3 : 3 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*].

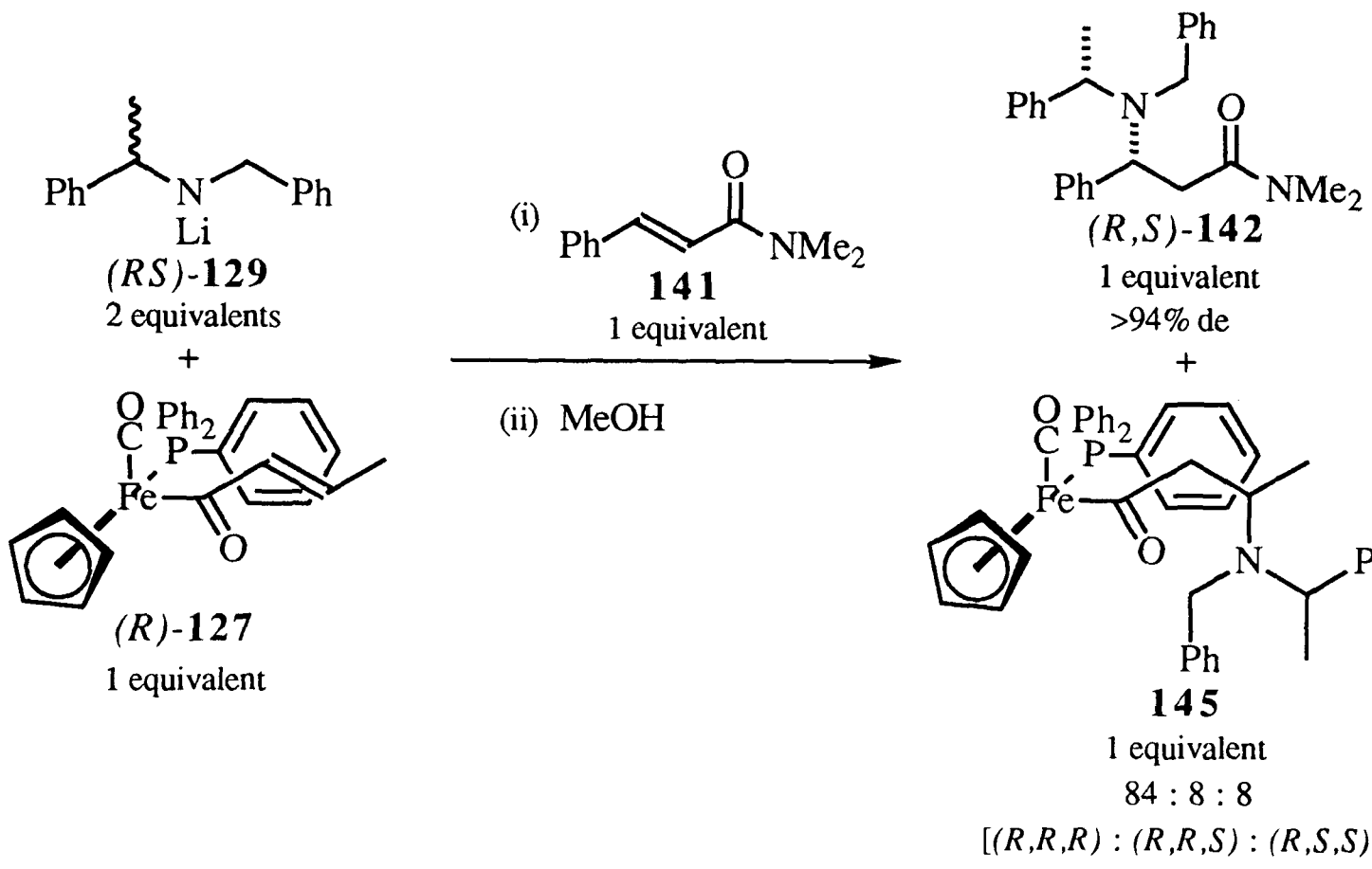
3 : Addition of one equivalent of *(RS)*-129 followed by one equivalent of 141 to the enolate *(R,R,R)*-146.



In the third experiment, butyllithium (0.1 mL, 0.16 mmol) was added to a stirred solution of *(R)*-(α-methylbenzyl)benzyl amine (**143**) (0.040 g, 0.19 mmol) in THF (15 mL) at 0°C, resulting in the formation of a pink-red solution of the lithium amide *(R)*-(**129**). After stirring at 0°C for 30 min and then for 1 h at -78°C, *(R)*-iron crotonyl complex (**127**) (0.077 g, 0.16 mmol) in THF (10 mL) at -78°C was added by cannula, resulting in the formation of a dark orange solution (**637**), and stirring was continued for 3 h at -78°C. A solution of *(RS)*-**129** was prepared [by the addition of butyllithium (0.1 mL, 0.16 mmol) to a solution of *(RS)*-**143** (0.041 g, 0.19 mmol) in THF (15 mL) at 0°C and stirring for 30 min at 0°C and then for 1 h at -78°C] and added by cannula to the reaction mixture. The reactants were stirred together at -78°C for 2 h. N,N-dimethyl cinnamide (**141**) (0.030 g, 0.17 mmol) in THF (10 mL) was added by cannula at -78°C and the orange solution was stirred for a further 2 h after which MeOH (1 mL) was added and the reaction mixture was warmed to room temperature. Removal of solvent *in vacuo*, addition of CH_2Cl_2 (30 mL) and filtration through alumina (10% deactivated) yielded (after removal of the solvent *in vacuo*) the crude product as an orange oil. ^1H NMR

spectroscopy of the crude product revealed that >90% conversion of **127** and ~80% conversion of **141**, to their respective Michael adducts (**145** and **142**), had occurred. **145** was formed as the *R,R,R* diastereomer, **142** was formed as the *SR,RS* diastereomer with a diastereomeric excess of >94%. Flash chromatography (silica, 1 : 1, Et_2O : petrol) enabled isolation of **142**. Measurement of the enantiomeric excess of **142** using the method described above indicated a value of 16% ee (enriched in the *S,R* enantiomer).

Addition of N,N-dimethyl cinnamide (141) to the complex formed between *(R)*-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH{=}CHCH_3$)](127) and lithium-[*(RS)*-α-methylbenzyl]benzyl amide (129).



Butyllithium (0.2 mL, 0.32 mmol) was added to a stirred solution of *(RS)*-(α-methylbenzyl)benzyl amine (**143**) (0.077 g, 0.36 mmol) in THF (15 mL) at 0°C, resulting in the formation of a pink-red solution of the lithium amide *(RS)*-(**129**). After stirring at 0°C for 30 min and then for 1 h at -78°C, *(R)*-iron crotonyl complex (**127**) (0.077 g, 0.16 mmol) in THF (10 mL) at -78°C was added by cannula and stirring was continued for 3 h at -78°C. Addition by cannula of N,N-dimethyl cinnamide (**141**) (0.028 g, 0.16 mmol) in

THF (10 mL) at -78°C was performed and the dark orange reaction mixture was stirred for a further 3 h at -78°C. MeOH (1 mL) was added and the reaction mixture was warmed to room temperature. Removal of solvent *in vacuo*, addition of CH_2Cl_2 (30 mL) and filtration through alumina (10% deactivated) yielded (after removal of the solvent *in vacuo*) the crude product as an orange oil. ^1H NMR spectroscopy of the crude product revealed that complete conversion of **127** and **141**, to their respective Michael adducts (**145** and **142**), had occurred. **145** was formed with a diastereomeric ratio of 84 : 8 : 8 [*(R,R,R)* : *(R,R,S)* : *(R,S,S)*], **142** was formed as the *R,S* diastereomer with a diastereomeric excess of >94%.

Addition of N,N-dimethyl cinnamide (141) to the complex formed between *(R)*-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=CHCH_3)](127) and lithium-[*(R)*-α-methylbenzyl]benzyl amide (129).

This experiment was performed as described above except that instead of using *(RS)*-**129**, *(R)*-**129** was added. Once again ^1H NMR spectroscopy of the crude product revealed that complete conversion of **127** and **141** to their respective Michael adducts (**145** and **142**) had occurred.

Chapter 7

Experimental

2-Hydroxymethyl-4,4-dimethoxybutyl acetate (149).

See reference 156.

3-Hydroxy-2-benzylpropyl acetate (86).

See Chapter 4 experimental for the preparation of this material.

3-Hydroxy-2-(1-methylnaphthyl)propyl acetate (91).

See Chapter 4 experimental for the preparation of this material.

Attempted racemisation of 86, 91 and 149 with triethylamine.

A large excess of triethylamine was added to the optically active monoacetate (**86**, **91** or **149**) in CH_2Cl_2. At various intervals samples were taken, the triethylamine and CH_2Cl_2 were removed *in vacuo*, and the specific rotation of recovered monoacetate (**86**, **91** or **149**) was measured. As shown in **Scheme 73**, no reduction in rotation was observed.

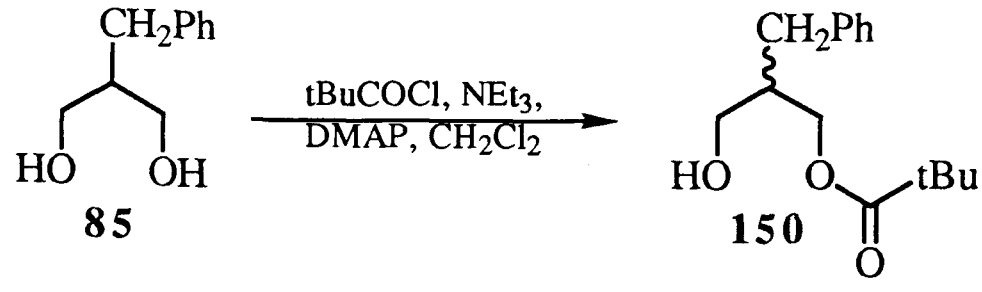
Attempted racemisation of 86 with potassium carbonate.

A large excess of K_2CO_3 was added to the monoacetate (**86**) in CH_2Cl_2 and the mixture was stirred at room temperature for 7 d. K_2CO_3 was removed by aqueous extraction. After drying ($MgSO_4$) and removal of solvent *in vacuo*, the specific rotation of the remaining monoacetate (**86**) was measured and found to be unchanged.

General Procedure for the pyridinium *para*-toluenesulphonate (PPTS) mediated racemisation of propan-1,3-diol derivatives.

The optically active propan-1,3-diol derivative (~ 1.0 mmol) and PPTS (~ 0.1 mmol) were stirred in CH_2Cl_2 (25 mL) at room temperature for 24 h. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The specific rotation of the recovered substrate was measured. When there had been no change in the specific rotation the process was repeated, this time stirring for 7 d.

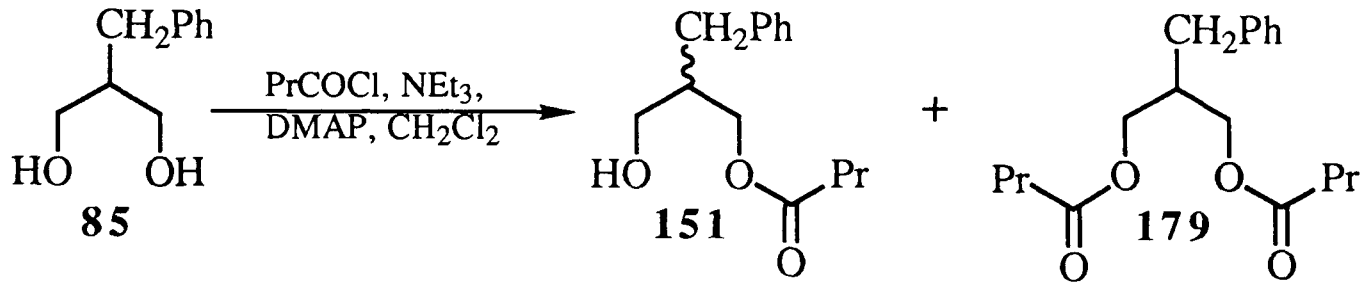
Preparation of 3-hydroxy-2-benzylpropyl trimethylacetate (150).



Trimethylacetyl chloride (2.2 g, 18.2 mmol) was added to a mixture of 2-benzylpropan-1,3-diol (**85**) (2.5 g, 15.1 mmol), triethylamine (2.2 g, 21.8 mmol) and DMAP (10 mg) in CH_2Cl_2 (100 mL). The reactants were stirred at room temperature for 16 h. After washing with saturated $NaHCO_3$ solution, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography (silica, 2 : 1, Et_2O : petrol) yielded recovered starting material (**85**) (0.50 g, 20%) and product (**150**) (2.49 g, 66%) as a colourless oil.

150 : Found: C, 72.0; H, 9.3. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%; $\nu_{max.}$ 3300 (O-H), 1722 (C=O) cm^{-1}; δ_H 7.27 [5H, m, Ph], 4.24, 4.07 [2H, ABX system, J_{AX} 4.2 Hz, J_{BX} 6.2 Hz, J_{AB} 11.3 Hz, CH_2OCO], 3.54 [2H, m, CH_2OH], 2.64 [2H, m, CH_2Ph], 2.17 [2H, m, CH and OH], 1.25 [9H, s, $(CH_3)_3$]; δ_C 179.8 [C=O], 139.8, 129.2, 128.6, 126.4 [Ph], 63.5 [CH_2OCO], 61.9 [CH_2OH], 42.6 [CH], 39.4 [$(CH_3)_3C$], 34.1 [CH_2Ph], 27.1 [$(CH_3)_3C$]; *m/z* 268 (M^++NH_4).

Preparation of 3-hydroxy-2-benzylpropyl butanoate (151).



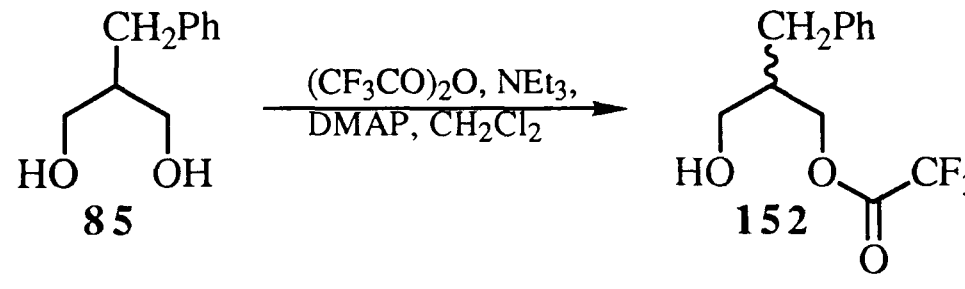
Butyryl chloride (1.2 g, 11.2 mmol) was added to a mixture of 2-benzylpropan-1,3-diol (**85**) (1.5 g, 9.0 mmol), triethylamine (1.3 g, 12.9 mmol) and DMAP (10 mg) in CH_2Cl_2 (100 mL). The reactants were stirred at room temperature for 16 h. After washing with saturated $NaHCO_3$ solution, the organic layer was dried ($MgSO_4$) and the solvent was

removed *in vacuo* Flash chromatography (silica, 2 : 1, Et_2O : petrol) yielded recovered starting material (**85**) (0.32 g, 21%), the required product (**151**) (0.82 g, 39%), as a colourless oil, and 2-benzylpropan-1,3-dibutanoate (**179**) (0.98 g, 36%) as a colourless oil.

151 : Found: C, 70.9; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%; $\nu_{max.}$ 3300 (O-H), 1729 (C=O) cm^{-1}; δ_H 7.27 [5H, m, Ph], 4.23, 4.09 [2H, ABX system, J_{AX} 4.5 Hz, J_{BX} 6.2 Hz, J_{AB} 11.2 Hz, CH_2OCO], 3.56 [2H, m, CH_2OH], 2.72, 2.62 [2H, ABX system, J_{AX} 7.8 Hz, J_{BX} 4.2 Hz, J_{AB} 12.1 Hz, CH_2Ph], 2.34 [2H, t, J 7.4 Hz, CH_2CO_2], 2.14 [2H, m, CH and OH], 1.69 [2H, m, CH_3CH_2], 0.98 [3H, t, J 7.4 Hz, CH_3]; δ_C 174.6 [C=O], 139.6, 129.2, 128.6, 126.3 [Ph], 63.7 [CH_2OCO], 61.9 [CH_2OH], 42.4 [CH], 36.0 [CH_2CO_2], 34.2 [CH_2Ph], 18.3 [CH_3CH_2], 13.5 [CH_3]; *m/z* 254 (M^++NH_4).

179 : Found: C, 71.0; H, 8.9. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.6%; $\nu_{max.}$ 1731 (C=O) cm^{-1}; δ_H 7.24 [5H, m, Ph], 4.09 [4H, m, 2 x CH_2OCO], 2.71 [2H, d, J 7.4 Hz, CH_2Ph], 2.34 [5H, m, 2 x CH_2CO_2 and CH], 1.66 [4H, m, 2 x CH_3CH_2], 0.97 [6H, t, J 7.2 Hz, 2 x CH_3]; δ_C 179.8 [2 x C=O], 138.9, 129.1, 128.7, 126.5 [Ph], 63.4 [2 x CH_2OCO], 39.1 [CH], 36.0 [2 x CH_2CO_2], 34.5 [CH_2Ph], 18.3 [2 x CH_3CH_2], 13.5 [2 x CH_3]; *m/z* 324 (M^++NH_4).

Preparation of 3-hydroxy-2-benzylpropyl trifluoroacetate (152).

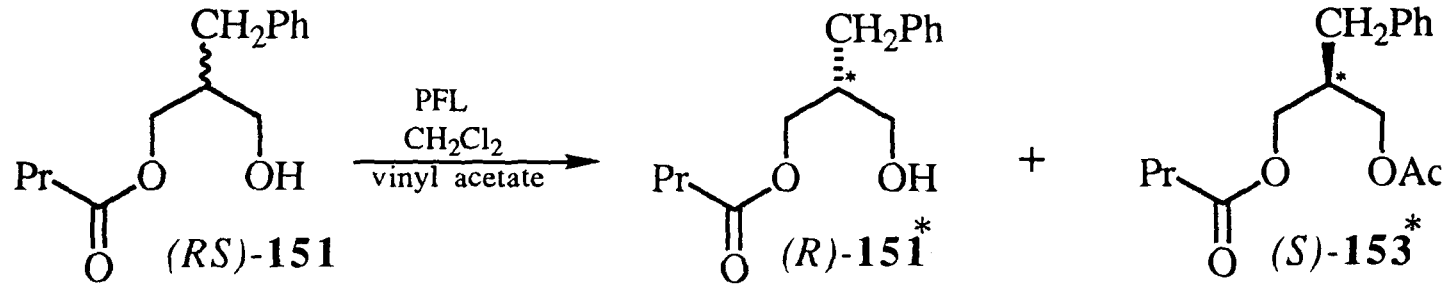


Trifluoroacetic anhydride (3.8 g, 18 mmol) was added to a mixture of 2-benzylpropan-1,3-diol (**85**) (2.5 g, 15.1 mmol), triethylamine (2.1 g, 21.1 mmol) and DMAP (10 mg) in CH_2Cl_2 (100 mL). The reactants were stirred at room temperature for 16 h. After washing with saturated $NaHCO_3$ solution, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography (silica, 3 : 1, Et_2O

: petrol) yielded recovered starting material (**85**) (0.51 g, 21%) and product (**152**) (1.56 g, 40%) as a colourless oil.

152 : Found: C, 56.5; H, 4.9. $C_{12}H_{13}O_3F_3$ requires C, 56.3; H, 5.1%; $\nu_{max.}$ 3300 (O-H), 1786 (C=O), 1171 (CF_3) cm^{-1}; δ_H 7.28 [5H, m, Ph], 4.45, 4.36 [2H, ABX system, J_{AX} 7.0 Hz, J_{BX} 6.0 Hz, J_{AB} 11.2 Hz, CH_2OCO], 3.71, 3.61 [2H, ABX system, J_{AX} 4.8 Hz, J_{BX} 6.1 Hz, J_{AB} 10.9 Hz, CH_2OH], 2.78, 2.67 [2H, ABX system, J_{AX} 7.8 Hz, J_{BX} 7.5 Hz, J_{AB} 13.6 Hz, CH_2Ph], 2.29 [1H, m, CH], 1.61 [1H, br, OH]; δ_C 175.2 [C=O], 157.5 [CF_3, q, J_{FC} 158 Hz] 138.5, 129.0, 128.7, 126.6 [Ph], 67.4 [CH_2OCO], 61.6 [CH_2OH], 41.9 [CH], 33.9 [CH_2Ph]; *m/z* 280 (M^++NH_4).

PFL mediated esterification of 151 to yield 2-benzyl-3-(methylethanoate)-propyl butanoate (153).



151 (0.29 g, 1.2 mmol), PFL (30 mg) and vinyl acetate (0.30 g, 3.5 mmol) were stirred in CH_2Cl_2 (100 mL) for 18 d. After filtration and removal of solvent *in vacuo*, ^1H NMR spectroscopy of the crude product showed a conversion of 38%. Flash chromatography (silica, 1 : 1, Et_2O : petrol) yielded recovered starting material [*(R)**-**151**] ($[\alpha]_D^{22}$ = +10.3 {c = 1.0, $CHCl_3$}) (0.15 g, 51%) and the diester [*(S)**-**153**] ($[\alpha]_D^{22}$ = -7.3 {c = 1.0, $CHCl_3$}) (0.10 g, 28%) as colourless oils. (*Tentatively assigned)

153 : Found: C, 69.0; H, 8.1. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%; $\nu_{max.}$ 1733 (C=O) cm^{-1}; δ_H 7.25 [5H, m, Ph], 4.11, 4.02 [4H, ABX system, J_{AX} 6.0 Hz, J_{BX} 6.0 Hz, J_{AB} 11.2 Hz, 2 x CH_2OCO], 2.71 [2H, d, J 7.3 Hz, CH_2Ph], 2.32 [3H, m, CH_2CO_2 and CH], 2.07 [3H, s, CH_3CO_2], 1.67 [2H, m, CH_3CH_2], 0.97 [3H, t, J 7.2 Hz, CH_3]; δ_C 173.8 [O=$COCH_2$], 171.2 [O=$COCH_3$] 138.9, 129.1, 128.7, 126.5 [Ph], 63.7

[$\underline{C}H_2OAc$], 63.4 [$\underline{C}H_2OCOCH_2$], 39.1 [$\underline{C}H$], 36.0 [$\underline{C}H_2CO_2$], 34.5 [$\underline{C}H_2Ph$], 20.6 [$\underline{C}H_3CO$], 18.3 [$CH_3\underline{C}H_2$], 13.5 [$\underline{C}H_3CH_2CH_2$]; *m/z* 296 (M^++NH_4).

Attempted Dynamic Kinetic Resolution of 151 using PPTS and PFL

For the attempted dynamic kinetic resolution, reaction conditions were as above except that PPTS (40 mg, 0.2 mmol) was added to the reaction mixture. The reactants were stirred for 61 d. ^{1}H NMR spectroscopy and TLC showed no sign of any reaction and on work up only recovered starting material (**151**) (83%) was isolated.

Test reaction performed to establish if PPTS inhibits PFL

2-(1-methylnaphthyl)propan-1,3-diol (**90**) (0.5 g, 2.3 mmol), PFL (27 mg), PPTS (40 mg, 0.2 mmol) and vinyl acetate (0.4 g, 4.7 mmol) were stirred in CH_2Cl_2 (50 mL). After 21 d stirring, ^{1}H NMR spectroscopy and TLC showed no sign of any reaction and on work up only starting material (**90**) (0.43 g, 86%) was recovered.

General Procedure for attempted racemisations of 91.

Optically active **91** (typically $[\alpha]_D^{22}$ = +27 [c = 1.0, $CHCl_3$]) (100 mg) was stirred with the "racemising agent" (0.1 equivalents) in CH_2Cl_2 (10 mL) for 7 d. After extraction with saturated $NaHCO_3$ solution followed by drying ($MgSO_4$), filtration and removal of solvent *in vacuo*, the specific rotation of the recovered starting material was measured. In the case of Py($OCOCF_3$) the specific rotation had decreased ($[\alpha]_D^{22} < 1$) indicating that racemisation had occurred. In all other cases Bu_4N(*p*-TSA), Na(*p*-TSA), DMAP, 2-hydroxypyridine and poly(4-vinyl pyridine) there had been no significant change in specific rotation.

Attempted PFL mediated acetylation of 2-benzylpropan-1,3-diol (85) in the presence of Py($OCOCF_3$).

The experiment was performed as described in the General Experimental except that Py($OCOCF_3$) (0.1 equivalents) was added to the reaction mixture. After stirring for 39 d

no sign of any reaction was detected by ^1H NMR spectroscopy or TLC. Aqueous extraction followed by drying ($MgSO_4$) of the organic layer, filtration and removal of solvent *in vacuo*, only yielded recovered starting material (**85**) (78%).

Racemisation of 91 using pyridinium washed Dowex®.

Dowex® 50X8-100 (1.0 g) was stirred in a strong aqueous solution (0.5 gmL^{-1}) of $Py(OCOCF_3)$. After stirring for 2 h, suction filtration was performed and the Dowex® was dried in a vacuum desicator. The pyridinium washed Dowex® (20 mg) was then stirred in CH_2Cl_2 (5 mL) with optically active **91** (50 mg) ($[\alpha]_D^{22}$ = +18 {c = 1.0, $CHCl_3$}) for 4 d. The reaction mixture was filtered and solvent was removed *in vacuo* to yield **91** (46 mg, 92%). Measurement of the specific rotation of the recovered starting material (**91**) indicated that racemisation had occurred ($[\alpha]_D^{22} < 1$).

Attempted PFL mediated acetylation of 85 in the presence of pyridinium washed Dowex®.

The experiment was performed as described in the General Experimental except that pyridinium washed Dowex® (20 mg) was added to the reaction mixture. After stirring for 64 d, the reaction was halted. Filtration, followed by removal of solvent *in vacuo*, yielded recovered starting material (**85**) (86%) only.

Attempted enzymic acetylation reactions in the presence of PPTS.

Experiments were performed as described in the General Experimental except that PPTS (0.1 equivalents) was added to the reaction mixture. After stirring each reaction for a period of time that would normally enable complete conversion of substrate to product (ranging from 5 to 21 d), each reaction was worked up in the normal manner. In all cases only starting material was recovered.

Chapter 8

Experimental

Preparation of *(RS,RS)*-[(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_2CH(OH)CH_3$)] (173).[136]

Butyllithium (2.6 mL, 4.2 mmol) was added to a solution of the *(RS)*-iron acetyl complex (**15**) (1.00 g, 2.2 mmol) in THF (30 mL) at -78°C. The resulting dark red solution was stirred for 1 h at -78°C. Diethyl aluminium chloride (2.0 M in toluene) (5.8 mL, 11.6 mmol) was then added and the reaction mixture was warmed to -40°C and stirred for 1 h. The mixture was cooled to -100°C and a solution of freshly distilled acetaldehyde (1.24 g, 28 mmol) in THF (10 mL) was added dropwise. After stirring for 2 h at -100°C, MeOH (1 mL) was added and the solution was warmed to room temperature. Removal of the solvent *in vacuo* was followed by addition of CH_2Cl_2 (20 mL). The organic layer was washed with saturated $NaHCO_3$ solution and then filtered through alumina (10% deactivated). After concentration, the crude product was obtained as a yellow solid. Flash chromatography (alumina, CH_2Cl_2) gave recovered starting material (**15**) (0.22 g, 22%) and the required product (**173**) (0.69 g, 63%) as a yellow solid with a diastereomeric ratio of 7 : 1 [*(RS,RS)* : *(RS,SR)*].

(RS,RS)-**173**[136] : δ_H 7.42 [15H, m, P$\underline{Ph}_3$], 4.45 [5H, s, $C_5\underline{H}_5$], 3.55 [1H, br s, O$\underline{H}$], 3.33 [1H, m, C$\underline{H}$OH], 2.83 [2H, m, C$\underline{H}_2$], 0.82 [3H, d, J 6.2 Hz, C$\underline{H}_3$].

Preparation of 1 : 1 mixture of *(RS,RS)*-173 and *(RS,SR)*-173.[136]

Butyllithium (4.5 mL, 7.2 mmol) was added to a solution of the *(RS)*-iron acetyl complex (**15**) (2.00 g, 4.4 mmol) in THF (30 mL) at -78°C. The resulting dark red solution was stirred for 1 h at -78°C. A solution of freshly distilled acetaldehyde (0.78 g, 17.7 mmol) in THF (10 mL) was added dropwise. After stirring for 2 h at -78°C, MeOH (1 mL) was added and the solution was warmed to room temperature. Removal of the solvent *in vacuo* was followed by addition of CH_2Cl_2 (20 mL) and filtration through alumina (10% deactivated). After concentration, the crude product was obtained as a yellow solid. Flash chromatography (alumina, CH_2Cl_2) gave the required product (**173**) (1.49 g, 68%) as a yellow solid with a diastereomeric ratio of ~ 1 : 1 [*(RS,RS)* : *(RS,SR)*].

(RS,SR)-**173**[139] : selected δ_H 4.44 [5H, s, $C_5\underline{H}_5$], 0.89 [3H, d, J 6.2 Hz, C$\underline{H}_3$].

Preparation of *(RS,RS)*-[(η^5-C_5H_5)Fe(CO)(PPh_3)($COCH_2CH(OAc)CH_3$)] (174).[140]

To a stirred solution of *(RS,RS)*-**173** (0.11 g, 0.2 mmol) in THF (20 mL) at -5°C was added methyllithium (1.5 M in Et_2O) (0.2 mL, 0.3 mmol). Stirring was continued for 1 h at -5°C and resulted in a colour change from orange to black and the evolution of a gas. Acetic anhydride (0.05 mL, 0.5 mmol) was added and the reactants were stirred together for 1 h during which time the colour reverted back to orange. After washing with saturated $NaHCO_3$, the organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography (alumina, 1 : 4, EtOAc : CH_2Cl_2) gave the required product (**174**) (0.06 g, 52%) as a yellow solid.

(RS,RS)-**174**[140] : δ_H 7.38 [15H, m, P<u>Ph</u>$_3$], 4.90 [1H, m, C<u>H</u>], 4.45 [5H, s, C_5<u>H</u>$_5$], 3.41 [1H, m, C<u>H</u>H], 2.63 [1H, m, CH<u>H</u>], 1.99 [3H, s, C<u>H</u>$_3$CO], 0.74 [3H, d, J 5.5 Hz, C<u>H</u>$_3$].

General procedure for enzymic esterification of 173.

Each enzyme (typically 0.10 g) was added to a stirred solution of *(RS,RS)* and *(RS,SR)*-**173** (0.10 g, 0.2 mmol) and vinyl acetate (0.10 g, 1.2 mmol) in CH_2Cl_2 (10 mL). The reactants were fully degassed and stirred for a period of 15 - 20 d under a nitrogen atmosphere at room temperature. Extent of reaction was monitored by ^{1}H NMR spectroscopy and TLC. Filtration of the reaction mixture (to remove the enzyme) was followed by removal of solvent and excess vinyl acetate *in vacuo*. The crude product was analysed by TLC and ^{1}H NMR spectroscopy.

A number of reactions were tried as outlined above using isopropenyl acetate as acyl donor (in place of vinyl acetate). Some experiments were also tried in neat vinyl acetate or isopropenyl acetate. In all cases no reaction was observed except as described below.

PPL mediated esterification of *(RS,RS)*-173.

To a stirred solution of *(RS,RS)*-**173** (1.19 g, 2.4 mmol) and vinyl acetate (1.3 g, 15.1 mmol) in CH_2Cl_2 (10 mL) was added PPL (1.5 g). The reactants were fully degassed and stirred for a period of 18 d under a nitrogen atmosphere at room temperature. Extent of reaction was monitored by ^1H NMR spectroscopy and TLC. Filtration of the reaction mixture (to remove the enzyme) was followed by removal of solvent and excess vinyl acetate *in vacuo*. TLC of the crude product revealed two components, one spot corresponded to the starting material (**173**) and the other possessed a similar R*f* value to the expected product (**174**). Flash chromatography (silica, 3 : 1, Et_2O : petrol) gave an unidentifiable yellow band (5 mg) and recovered starting material (**173**) (1.03 g, 87%). Measurement of the specific rotation of the unidentified product and the recovered starting material was performed (c = 0.1, benzene) and in both cases $[\alpha]_D^{22} = 0.0$.

References

1. "Chirality in Drug Design and Synthesis", ed. C. Brown, Academic Press, 1990.

2. R. T. Williams, *Arch. Environ. Health,* 1968, **16**, 493.

3. D. E. Drayer, *Clin. Pharmacol. Ther.,* 1986, **40**, 125.

4. See for example: (a) R. Sheldon, *Chemistry & Industry,* 1990, 212; (b) G. M. Ramos Tombo and D. Bellus, *Angew. Chem., Int. Ed. Engl.,* 1991, **30**, 1193; (c) J. W. Scott, *Top. Stereochem.*, 1989, **19**, 209.

5. (a) H.B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249; (b) C.J. Sih and S. H. Wu, *Top. Stereochem.*, 1989, **19**, 63.

6. See for example: J. M. Brown and S. G. Davies, *Nature*, 1989, **342**, 631; J. Crosby, *Tetrahedron*, 1991, **47**, 4789; "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press, 1983 - 1985, volumes 1 - 5.

7.* (a) C. S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294; (b) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237; (c) T. Hayashi, K. Kanehira, T. Hioki and M. Kumada, *Tetrahedron Lett.*, 1981, **22**, 137.

8. M. Kitamura, I. Kasahara, K. Manabe, R. Noyori and H. Takaya, *J. Org. Chem.*, 1988, **53**, 708.

9. N. Matsuo and N. Ohno, *Tetrahedron Lett.*, 1985, **26**, 5533.

10. R. Chincilla, C. Nájera, M. Yus and A. Heumann, *Tetrahedron: Asymmetry*, 1991, **2**, 101.

11. (a) M. Polla and T. Frejd, *Tetrahedron*, 1991, **47**, 5883; (b) T. R. Nieduzak and A. A. Carr, *Tetrahedron: Asymmetry*, 1990, **1**, 535; (c) D. Basavaiah, P. Rama Krishna and T. K. Bharathi, *Tetrahedron Lett.*, 1990, **31**, 4347.

12. R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi and H. Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134.

13. J. D. Morrison in "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press, 1983, volume 1, p1.

*For more advanced numerical integration methods see for example: L. W. Johnson and R. D. Wiess, "Numerical Analysis", Addison-Wesley Publishing, 1977.

14. S. Takahashi, T. Ohashi, Y. Kii, H. Kumagai and H. Yamada, *J. Ferment. Technol.*, 1979, **57**, 328; S. G. Davies, D. Middlemiss, A. Naylor and M. Wills, *J. Chem. Soc., Chem. Commun.*, 1990, 797; H. S. Bevinakatti, R. V. Newadkar and A. A. Banerji, *J. Chem. Soc., Commun.*, 1990, 1091; M. Inagaki, J. Hiratake, T. Nishioka and J. Oda, *J. Am. Chem. Soc.*, 1991, **113**, 9360; J. P. Genet, C. Pinel, S. Mallart, S. Juge, S. Thorimbert and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1991, **2**, 555; M. Inagaki, A. Hatanaka, M. Mimura, J. Hiratake, T. Nishioka and J. Oda, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 111; R. L. Gu, I. S. Lee and C. J. Sih, *Tetrahedron Lett.*, 1992, **33**, 1953; M. Yamagishi, Y. Yamada, K. Ozaki, T. Da-te, K. Okamura, M. Suzuki and K. Matsumoto, *J. Org. Chem.*, 1992, **57**, 1568.

15. G. Fülling and C. J. Sih, *J. Am. Chem. Soc.*, 1987, **109**, 2845.

16. D. W. Brooks, M. Wilson and M. Webb, *J. Org. Chem.*, 1987, **52**, 2244; A. J. J. Straathof, J. L. L. Rakels and J. J. Heijnen, *Biocatalysis,* 1990, **4**, 89.

17. K. Stanley and M. C. Baird, *J. Am. Chem. Soc.*, 1975, **97**, 6598.

18. S. C. Preston, D. Phil. Thesis, University of Oxford, 1989, p73.

19. F. VanMiddlesworth, Y. F. Wang, B. Zhou, D. DiTullio and C. J. Sih, *Tetrahedron Lett.*, 1985, **26**, 961; P. Kalaritis, R. W. Regenye, J. J. Partridge and D. L. Coffen, *J. Org. Chem.*, 1990, **55**, 812; T. Sugai, H. Kakeya, and H. Ohta, *J. Org. Chem.*, 1990, **55**, 4643; B. D. Johnston, B. Morgan, A. C. Oehlschlager and S. Ramaswamy, *Tetrahedron: Asymmetry*, 1991, **2**, 377; Y. Naoshima, Y. Munakata, S. Yoshida and A. Funai, *J. Chem. Soc. Perkin Trans. 1*, 1991, 549; T. Tsukamoto, T. Yoshiyama and T. Kitazume, *Tetrahedron: Asymmetry* , 1991, **2**, 759.

20. K. A. Babiak, J. S. Ng, J. H. Dygos, C. L. Weyker, Y. F. Wang and C. H. Wong, *J. Org. Chem.,* 1990, **55**, 3377.

21. S. H. Hsu, S. S. Wu, Y. F. Wang and C. H. Wong, *Tetrahedron Lett.*, 1990, **31**, 6403; T. Yamazaki, N. Okamura and T. Kitazume, *Tetrahedron: Asymmetry*, 1990, **1**, 521; Y. Yamazaki, N. Morohashi and K. Hosono, *Biotechnology Lett.*, 1991,

13, 81; A. J. M. Janssen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, 1991, **47**, 7409; E. Fukusaki, S. Senda, Y. Nakazono and T. Omata, *Tetrahedron*, 1991, **47**, 6223; T. Sugai, T. Yokochi, N. Watanabe and H. Ohta, *Tetrahedron*, 1991, **47**, 7227; G. Carrea, B. Danieli, G. Palmisano, S. Riva and M. Santagostino, *Tetrahedron: Asymmetry*, 1992, **3**, 775.

22. D. G. Drueckhammer, C. F. Barbas III, K. Nozaki and C. H. Wong, *J. Org. Chem.*, 1988, **53**, 1607.

23. (a) S. H. Wu, L. Q. Zhang, C. S. Chen, G. Girdaukas and C. J. Sih, *Tetahedron Lett.*, 1985, **26**, 4323; (b) D. H. G. Crout, V. S. B. Gaudet, K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1986, 808; (c) K. Laumen, D. Breitgoff, R. Seemayer and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1989, 148.

24. M. A. Djadchenko, K. K. Pivnitsky, F. Theil and H. Schick, *J. Chem. Soc. Perkin Trans. 1*, 1989, 2001; R. J. Kazlauskas, *J. Am. Chem. Soc.*, 1989, **111**, 4953; E. L. A. Macfarlane, S. M. Roberts and N. J. Turner, *J. Chem. Soc., Chem. Commun.*, 1990, 569; Z. W. Guo, S. H. Wu, C. S. Chen, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1990, **112**, 4942; P. W. Fowler, E. L. A. Macfarlane and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1991, 453; E. L. A. Macfarlane, F. Rebolledo, S. M. Roberts and N. J. Turner, *Biocatalysis*, 1991, **5**, 13; F. Theil, S. Ballschuh, A. Kunath and H. Schick, *Tetrahedron: Asymmetry*, 1991, **2**, 1031; R. Seemayer and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1991, 49; G. Caron and R. J. Kazlauskas, *J. Org. Chem.*, 1991, **56**, 7251; C. S. Chen and Y. C. Liu, *J. Org. Chem.*, 1991, **56**, 1966; F. Theil, A. Kunath and H. Schick, *Tetrahedron Lett.*, 1992, **33**, 3457

25. H. Kakeya, N. Sakai, T. Sugai and H. Ohta, *Tetrahedron Lett.*, 1991, **32**, 1343.

26. S. M. Brown, S. G. Davies and J. A. A. de Sousa, *Tetrahedron: Asymmetry*, 1991, **2**, 511.

27. W. R. Roush and R. J. Brown, *J. Org. Chem.*, 1982, **47**, 1371; W. R. Roush and R.J. Brown, *J. Org. Chem.*, 1983, **48**, 5093; L. Dai, B. Lou and Y. Zhang, *J. Am.*

Chem. Soc., 1988, **110**, 5195; Y. Lu, C. Miet, N. Kunesch and J. Poisson, *Tetrahedron: Asymmetry*, 1990, **1**, 707; I. Yamakawa, H. Urabe, Y. Kobayashi and F. Sato, *Tetrahedron Lett.*, 1991, **32**, 2045.

28. T. Yamazaki, J. Haga and T. Kitazume, *Bioorg. & Med. Chem. Lett.*, 1991, **1**, 271.

29. T. Sugai, D. Sakuma, N. Kobayashi and H. Ohta, *Tetrahedron*, 1991, **47**, 7237.

30. K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1986, 1298; Y. F. Wang, J. J. Lalonde, M. Momongan, D. E. Bergbreiter and C. H. Wong, *J. Am. Chem. Soc.*, 1988, **110**, 7200; S. H. Wu, L. C. Lo, S. T. Chen and K. T. Wang, *J. Org. Chem.*, 1989, **54**, 4220; D. L. Hughes, J. J. Bergan, J. S. Amato, M. Bhupathy, J. L. Leazer, J. M. McNamara, D. R. Sidler, P. J. Reider and E. J. J. Grabowski, *J. Org. Chem.*, 1990, **55**, 6252; F. Theil, H. Schick, M. A. Lapitskaya and K. K. Pivnitsky, *Liebigs Ann. Chem.*, 1991, 195; F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417; A. Ishikawa and T. Katsuki, *Tetrahedron Lett.*, 1991, **32**, 3547; K. J. Harris, Q. M. Gu, Y. E. Shih, G. Girdaukas and C. J. Sih, *Tetrahedron Lett.*, 1991, **32**, 3941; H. E. Schink and J. E. Bäckvall, *J. Org. Chem.*, 1992, **57**, 1588; H. J. Gais, H. Hemmerle and S. Kossek, *Synthesis*, 1992, 169.

31. Y. F. Wang, C. S. Chen, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1984, **106**, 3695; Y. F. Wang, C. S. Chen, G. Girdaukas and C. J. Sih in "Enzymes in Organic Synthesis" (Ciba Foundation Symposium 111), eds. R. Potter and S. Clark, Pitman 1985, p128.

32. S. Hatakeyama, K. Sakurai and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1985, 1759; B. Häfele, D. Schröter and V. Jäger, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 87; S. L. Schreiber, T. S. Schreiber and D. B. Smith, *J. Am. Chem. Soc.*, 1987, **109**, 1525; D. B. Smith, Z. Wang and S. L. Schreiber, *Tetrahedron*, 1990, **46**, 4793; V. Jäger, D. Schröter and B. Koppenhoefer, *Tetrahedron*, 1991, **47**, 2195.

33. J. M. Chong and K. K. Sokoll, *Tetrahedron Lett.*, 1992, **33**, 879.

34. K. Burgess and I. Henderson, *Tetrahedron: Asymmetry*, 1990, **1**, 57; K. Burgess, J. Cassidy and I. Henderson, *J. Org. Chem.*, 1991, **56**, 2050.

35. K. K. C. Liu, K. Nozaki and C. H. Wong, *Biocatalysis*, 1990, **3**, 169.

36. This programme is a modified version of a programme written by Dr. S. M. Brown.

37. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974.

38. (a) R. A. Johnson and K. B. Sharpless in "Comprehensive Organic Synthesis", ed. B. M. Trost, Pergamon, 1991, volume 7, p389; (b) M. G. Finn and K. B. Sharpless in "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press, 1985, volume 5, p247; (c) B. E. Rossiter in "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press, 1985, volume 5, p193.

39. B. E. Rossiter, T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 464.

40. K. B. Sharpless, *Chem. Br.*, 1986, **22**, 38.

41. M. J. Schweiter and K. B. Sharpless, *Tetrahedron Lett.*, 1985, **26**, 2543.

42. S. G. Davies and S. M. Brown, unpublished results.

43. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136.

44. A similar strategy has been used by Dr. S. M. Brown: see reference 26.

45. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.

46. J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

47. K. Mori, S. Tamada, M. Uchida, N. Mizumachi, Y. Tachibana and M. Matsui, *Tetrahedron*, 1978, **34**, 1901.

48. See for example: H. G. Davies, R. H. Green, D. R. Kelly and S. M. Roberts, "Biotransformations in Preparative Organic Chemistry", Academic Press, 1989; D. H. G. Crout and M. Christen in "Modern Synthetic Methods", ed. R. Scheffold, Springer Verlag, 1989; A. M. Kilbanov, *Acc. Chem. Res.*, 1990, **23**, 114; N. J. Turner, *Nat. Prod. Rep.*, 1989, 625.

49. C. J. Suckling in "Enzyme Chemistry: impact and applications", ed. C. J. Suckling, Chapman & Hall, 1990 (second edition), p98.

50. "Selected Organic Synthesis", I. Fleming, Wiley, 1973, p36.

51. W. Boland, C. Fröβl and M. Lorenz, *Synthesis*, 1991, 1049.

52. T. Sugahara, I. Satoh, O. Yamada and S. Takano, *Chem. Pharm. Bull.*, 1991, **39**, 2758.

53. R. Bovara, G. Carrea, L. Ferrara and S. Riva, *Tetrahedron: Asymmetry*, 1991, **2**, 931.

54. K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 598; K. Laumen, D. Breitgoff and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 1459.

55. Z. F. Xie, H. Suemune and K. Sakai, *J. Chem. Soc., Chem. Commun.*, 1988, 1638.

56. K. Mori and Y. Takahashi, *Liebigs Ann. Chem.*, 1991, 1057.

57. Y. F. Wang and C. J. Sih, *Tetrahedron Lett.*, 1984, **25**, 4999.

58. K. Mori and N. Chiba, *Liebigs Ann. Chem.*, 1989, 957.

59. (a) S. Atsuumi, M. Nakano, Y. Koike, S. Tanaka, M. Ohkubo, T. Yonezawa, H. Funabashi, J. Hashimoto and H. Morishima, *Tetrahedron Lett.*, 1990, **31**, 1601; (b) K. Tsuji, Y. Terao and K. Achiwa, *Tetrahedron Lett.*, 1989, **30**, 6189.

60. Y. Terao, M. Murata, K. Achiwa, T. Nishio, M. Akamtsu and M. Kamimiura, *Tetrahedron Lett.*, 1988, **29**, 5173.

61. T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake and A. Oku, *J. Am. Chem. Soc.*, 1987, **109**, 527.

62. M. Ihara, M. Takahashi, N. Taniguchi, K. Fukumoto and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 619; M. Ihara, M. Takahashi, N. Taniguchi, K. Yasui, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1989, 897.

63. F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin and P. Szmulik, *Tetrahedron*, 1985, **41**, 1347.

64. G. Guanti, L. Banfi and E. Narisano, *Tetrahedron: Asymmetry*, 1990, **1**, 721; G. Guanti, E. Narisano, T. Podgorski, S. Thea and A. Williams, *Tetrahedron*, 1990, **46**, 7081; R. Lattman, O. Ghisalba, D. Gygax, H. P. Schär and E. Schmidt,

Biocatalysis, 1990, **3**, 137; B. Wirz, R. Schmid and W. Walther, *Biocatalysis*, 1990, **3**, 159; E. Didier, B. Loubinoux, G. M. Ramos Tombo and G. Rihs, *Tetrahedron*, 1991, **47**, 4941.

65. G. M. Ramos Tombo, H. P. Schär, X. Fernandez, I. Busquets and O. Ghisalba, *Tetrahedron Lett.*, 1986, **27**, 5707.

66. A. H. Djerourou and L. Blanco, *Tetrahedron Lett.*, 1991, **32**, 6325.

67. E. Santeniello, P. Ferraboschi and P. Grisenti, *Tetrahedron Lett.*, 1990, **31**, 5657; P. Grisenti, P. Ferraboschi, A. Manzocchi and E. Santeniello, *Tetrahedron*, 1992, **48**, 3827.

68. P. Ferraboschi, P. Grisenti and E. Santeniello, *Synlett*, 1990, 545.

69. P. T. Stephenson, D. Phil. Thesis, University of Oxford, 1990.

70. J. H. Bordon, J. R. Handley, J. A. McLean, R. M. Silverstein, L. Chong, K. N. Slessor, B. D. Johnston and H. R. Schuler, *J. Chem. Ecol.*, 1980, **6**, 445.

71. J. H. Borden, L. Chong, J. A. McLean, K. N. Slessor and K. Mori, *Science*, 1976, **192**, 894.

72. K. J. Byrne, A. A. Swigar, R. M. Silverstein, J. H. Borden and E. Stokkink, *J. Insect Physiol.*, 1974, **20**, 1895.

73. K. Mori, *Tetrahedron*, 1975, **31**, 3011.

74. H. R. Schuler and K. N., *Can. J. Chem.*, 1977, **55**, 3280.

75. B. D. Johnston and K. N. Slessor, *Can. J. Chem.*, 1979, **57**, 233.

76. C. W. Bradshaw, W. Hummel and C. H. Wong, *J. Org. Chem.*, 1992, **57**, 1532.

77. C. W. Bradshaw, H. Fu, G. J. Shen and C. H. Wong, *J. Org. Chem.*, 1992, **57**, 1526.

78. E. Keinan, E. K. Hafeli, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 162.

79. A. Belan, J. Bolte, A. Fauve, J. G. Gourcy and H. Veschambre, *J. Org. Chem.*, 1987, **52**, 256.

80. K. Mori, *Tetrahedron*, 1981, **37**, 1341.

81. K. Nakamura, T. Kitayama, Y. Inoue and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 91.

82. T. M. Stokes and A. C. Oehlschlager, *Tetrahedron Lett.*, 1987, **28**, 2091.

83. B. Cambou and A. M. Klibanov, *J. Am. Chem. Soc.*, 1984, **106**, 2687.

84. S. Liang and L. A. Paquette, *Tetrahedron: Asymmetry*, 1990, **1**, 445.

85. F. Secundo, S. Riva and G. Carrea, *Tetrahedron: Asymmetry*, 1992, **3**, 267.

86. G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, S. Poli, F. Gardini and M. E. Guerzoni, *Tetrahedron: Asymmetry*, 1992, **3**, 107; G. Fantin, M. Fogagnolo, M. E. Guerzoni, E. Marotta, A. Medici and P. Pedrini, *Tetrahedron: Asymmetry*, 1992, **3**, 947; P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *J. Chem. Soc. Perkin Trans. 1*, 1992, 1159.

87. P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1.

88. G. Wittig and U. Thiele, *Liebigs Ann. Chem.*, 1969, **726**, 1.

89. J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 1980, **45**, 755.

90. M. Asami, *Chem. Lett.*, 1984, 829.

91. K. Mori, B. G. Hazra, R. J. Pfeiffer, A. K. Gupta and B. S. Lindgren, *Tetrahedron*, 1987, **43**, 2249.

92. H. Kim, R. Shirai, H. Kawasaki, M. Nakajima and K. Koga, *Heterocycles*, 1990, **30**, 307.

93. J. A. Marshall and J. Lebreton, *Tetrahedron Lett.*, 1987, **28**, 3323.

94. L. Duhamel, A. Ravard, J. C. Plaquevent and D. Davoust, *Tetrahedron Lett.*, 1987, **28**, 5517.

95. P. Coggins and N. S. Simpkins, *Synlett*, 1991, 515; P. Coggins and N. S. Simpkins, *Synlett*, 1992, 313.

96. J. M. Hawkins and G. C. Fu, *J. Org. Chem.*, 1986, **51**, 2820; K. Rudolf, J. M. Hawkins, R. J. Loncharich and K. N. Houk, *J. Org. Chem.*, 1988, **53**, 3879.

97. J. M. Hawkins and T. A. Lewis, *J. Org. Chem.*, 1992, **57**, 2114.

98. S. G. Davies and O. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1990, 1554.

99. S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.

100. S. G. Davies and O. Ichihara, personal communication.

101. K. Gregory, P. von Ragué Schleyer and R. Snaith, *Advances in Inorganic Chemistry*, 1991, **37**, 47.

102. N. D. R. Barnett, R. E. Mulvey, W. Clegg and P. A. O'Neil, *J. Am. Chem. Soc.*, 1991, **113**, 8187; P. G. Williard and Q. Y. Liu, *J. Am. Chem. Soc.*, 1991, **114**, 348.

103. For leading references see: F. E. Romesberg, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 5751; P. L. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 9575; D. J. Gallagher, S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1992, **114**, 5872.

104. For leading references see: J. S. DePue and D. B. Collum, *J. Am. Chem. Soc.*, 1988, **110**, 5518; E. M. Arnett and K. D. Moe, *J. Am. Chem. Soc.*, 1991, **113**, 7288.

105. See for example: A. M. Sapse, E. Kaufmann, P. von Ragué Schleyer and R. Gleiter, *Inorg. Chem.*, 1984, **23**, 1569; A. M. Sapse, K. Raghavachari, P. von Ragué Schleyer and E. Kaufmann, *J. Am. Chem. Soc.*, 1985, **107**, 6483; F. E. Romesberg and D. B. Collum, *J. Am. Chem. Soc.*, 1992, **114**, 2112.

106. D. Barr, D. J. Berrisford, R. V. H. Jones, A. M. Z. Slawin, R. Snaith, J. F. Stoddart and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1044.

107. D. Mootz, A. Zinnius and B. Böttcher, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 378; R. D. Rogers, J. L. Atwood and R. Grüning, *J. Organomet. Chem.*, 1978, **157**, 229.

108. M. F. Lappert, M. J. Slade, A. Singh, J. L. Atwood, R. D. Rogers and R. Shakir, *J. Am. Chem. Soc.*, 1983, **105**, 302.

109. (a) D. R. Armstrong, D. Barr, W. Clegg, S. R. Drake, R. J. Singer, R. Snaith, D. Stalke and D. S. Wright, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1707; (b) R. E. Mulvey, *Chem. Soc. Rev.*, 1991, **20**, 167.

110. D. Sato, H. Kawasaki, I. Shimada, Y. Arata, K. Okamura, T. Date and K. Koja, *J. Am. Chem. Soc.*, 1992, **114**, 761.

111. D. Barr, W. Clegg, R. E. Mulvey and R. Snaith, *J. Chem. Soc., Chem. Commun.*, 1984, 285.

112. D. R. Armstrong, R. E. Mulvey, G. T. Walker, D. Barr, R. Snaith, W. Clegg and D. Reed, *J. Chem. Soc., Dalton Trans.*, 1988, 617.

113. D. Reed, D. Barr, R. E. Mulvey and R. Snaith, *J. Chem. Soc., Dalton Trans.*, 1986, 557.

114. D. Barr, W. Clegg, R. E. Mulvey and R. Snaith, *J. Chem. Soc., Chem. Commun.*, 1984, 287.

115. L. M. Jackman and L. M. Scarmoutzos, *J. Am. Chem. Soc.*, 1987, **109**, 5348.

116. B. Y. Kimura and T. L. Brown, *J. Organomet. Chem.*, 1971, **26**, 57.

117. W. Bauer and D. Seebach, *Helv. Chim. Acta*, 1984, **67**, 1972.

118. A. S. Galiano-Roth and D. B. Collum, *J. Am. Chem. Soc.*, 1989, **111**, 6772.

119. S. G. Davies and I. A. S. Walters, personal communication.

120. C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami and H. B. Kagan, *J. Am. Chem. Soc.*, 1986, **108**, 2353. For further examples see: M. Kitamura, S. Okada, S. Suga and R. Noyori, *J. Am. Chem. Soc.*, 1989, **111**, 4028; M. Terada, K. Mikami and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1990, 1623; C. Bolm, *Tetrahedron: Asymmetry*, 1991, **2**, 701; K. Tanaka, J. Matsui, Y. Kawabata, H. Suzuki and A. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1991, 1632.

121. D. Parker and R. J. Taylor, *Tetrahedron*, 1987, **43**, 5451.

122. F. Thiel, H. Schick, G. Winter and G. Reck, *Tetrahedron*, 1991, **47**, 7569.

123. S. G. Davies, *Aldrichimica Acta*, 1990, **23**, 31; S. G. Davies, *Pure Appl. Chem.*, 1988, **60**, 13.

124. S. G. Davies, I. M. Dordor-Hedgecock, K. H. Sutton, J. C. Walker, R. H. Jones and K. Prout, *Tetrahedron*, 1986, **42**, 5123.

125. P. W. Ambler and S. G. Davies, *Tetrahedron Lett.*, 1988, **29**, 6983.

126. H. Brunner and E. Schmidt, *J. Organomet. Chem.*, 1972, **36**, C18; H. Brunner and J. Strutz, *Z. Naturforsch.*, 1974, **29B**, 446.

127. S. C. Case-Green, D. Phil. Thesis, University of Oxford, 1991.

128. See reference 98.

129. See for example: A. Ratajczak and B. Misterkiewicz, *Chemistry & Industry*, 1976, 902; Y. I. Sokolov, L. L. Troitskaya and T. I. Rozhkova, *Gazz. Chim. Ital.*, 1987, **117**, 525; Y. Yamazaki and K. Hosono, *Tetrahedron Lett.*, 1989, **30**, 5313; S. Top, G. Jaouen, C. Baldoli, P. Del Buttero and S. Maiorana, *J. Organomet. Chem.*, 1991, **413**, 125; A. D. Ryabov, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 931.

130. Y. Yamazaki and K. Hosono, *Agric. Biol. Chem.*, 1988, **52**, 3239.

131. K. Nakamura, K. Ishihara, A. Ohno, M. Uemura, H. Nishimura and Y. Hayashi, *Tetrahedron Lett.*, 1990, **31**, 3603.

132. N. W. Boaz, *Tetrahedron Lett.*, 1989, **30**, 2061.

133. T. Itoh and T. Ohta, *Tetrahedron Lett.*, 1990, **31**, 6407; T. Itoh and T. Ohta, *Chem. Lett.*, 1991, 217; J. M. Chong and E. K. Mar, *Tetrahedron Lett.*, 1991, **32**, 5683.

134. N. W. Alcock, D. H. G. Crout, C. M. Henderson and S. E. Thomas, *J. Chem. Soc., Chem. Commun.*, 1988, 746.

135. For a similar approach see: E. Holmberg, E. Dahlen, T. Norin and K. Hult, *Biocatalysis*, 1991, **4**, 305.

136. S. G. Davies, I. M. Dordor-Hedgecock, P. Warner, R. H. Jones and K. Prout, *J. Organomet. Chem.*, 1985, **285**, 213.

137. (a) C. Feichter, K. Faber and H. Griengl, *Biocatalysis*, 1990, **3**, 145; (b) D. O'Hagan and N. A. Zaidi, *J. Chem. Soc. Perkin Trans. 1*, 1992, 947; (c) J. T. Lin, T. Yamazaki and T. Kitazume, *J. Org. Chem.*, 1987, **52**, 3211.

138. S. G. Davies, R. J. C. Easton, J. C. Walker and P. Warner, *Tetrahedron*, 1986, **42**, 175.

139. L. S. Liebeskind, M. E. Welker and R. W. Fengl, *J. Am. Chem. Soc.*, 1986, **108**, 6328.

140. L. S. Liebeskind, R. W. Fengl and M. E. Welker, *Tetrahedron Lett.*, 1985, **26**, 3075.

141. D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Pergamon, 1988 (third edition).

142. D. F. Shriver and M. A. Dreszdon, "The Manipulation of Air-Sensitive Compounds", Wiley, 1986.

143. K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.

144. G. Magnusson and S. Thorén, *J. Org. Chem.*, 1973, **38**, 1380.

145. C. J. Pouchert, "The Aldrich Library of NMR Spectra", The Aldrich Chemical Company, 1983 (second edition), volume 1, p941.

146. E. A. Hill, M. L. Gross, M. Stasiewicz and M. Manion, *J. Am. Chem. Soc.*, 1969, **91**, 7381.

147. H. L. Holland, E. J. Bergen, P. C. Chenchaiah, S. H. Khan, B. Munoz, R. W. Ninniss and D. Richards, *Can. J. Chem.*, 1987, **65**, 502.

148. T. Hayashi, Y. Matsumoto and Y. Ito, *J. Am. Chem. Soc.*, 1989, **111**, 3426.

149. B. K. Wasson, C. H. Gleason, I. Levi, J. M. Parker, L. M. Thompson and C. H. Yates, *Can. J. Chem.*, 1961, **39**, 923.

150. S. Tazuke and F. Banba, *Macromolecules*, 1976, **9**, 451.

151. Reference 59a reports a specific rotation for compounds **91** and **94** but gives no details of characterisation.

152. C. M. Cain, R. P. C. Cousins, G. Coumbarides and N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523.

153. O. Tsuge, K. Sone, S. Urano and K. Matsuda, *J. Org. Chem.*, 1982, **47**, 5171.

154. Stereochemistry assigned by analogy with that shown in reference 99.

155. Stereochemistry assigned by analogy with that shown in reference 98.

156. I thank Dr. P. T. Stephenson for a donation of this material (prepared as in reference 69).

Appendix 1

Computer Model used to calculate the outcome of Kinetic Resolutions using Scalemic Starting Material.

The programme was written on an Apple Macintosh Computer using Microsoft Basic.

Listing:

```
10 INPUT "% Enantiomeric excess of starting material =";SM
20 IF SM>100 GOTO 360
30 IF SM<-100 GOTO 360
40 INPUT "Stereoselectivity factor =";E
50 IF E=0 GOTO 360
60 INPUT "Number of points to be displayed =";D
70 EE=SM/100
80 A=1/(D-1)
90 RP=0
100 SP=0
110 B=0
120 RSM=((1+EE)/2)
130 SSM=(1-RSM)
140 PRINT "  %convn  %eeSM  %eeprod"
150 FOR Z=.001 TO .999 STEP .001
160 N=((E*RSM)+(SSM))
170 RPF=((.001*(RSM*E))/N)
180 SPF=((.001*SSM)/N)
190  RSM=RSM-RPF
200  SSM=SSM-SPF
210 RP=RP+RPF
220 SP=SP+SPF
230 C=100*Z
240 IF Z=.999 GOTO 260
250 IF Z>=B GOTO 260 ELSE 300
260 B=B+A
270 EESM=(100*((RSM-SSM)/(RSM+SSM)))
280 EEP=(100*((RP-SP)/(RP+SP)))
290 PRINT USING  "####.##";C,EESM,EEP
300 NEXT Z
310 PRINT "Initial % ee of starting material =";SM
320 PRINT "Stereoselectivity  factor=";E
330 FOR JdS = 1 TO 10000
340 NEXT JdS
350 END
360 PRINT "Invalid value - programme stopped"
370 FOR JdS = 1 TO 10000
380 NEXT JdS
390 END
```

Example of Input:

```
% Enantiomeric excess of starting material =? 50

Stereoselectivity factor =? 10

Number of points to be displayed =? 11
```

Example of Output:*

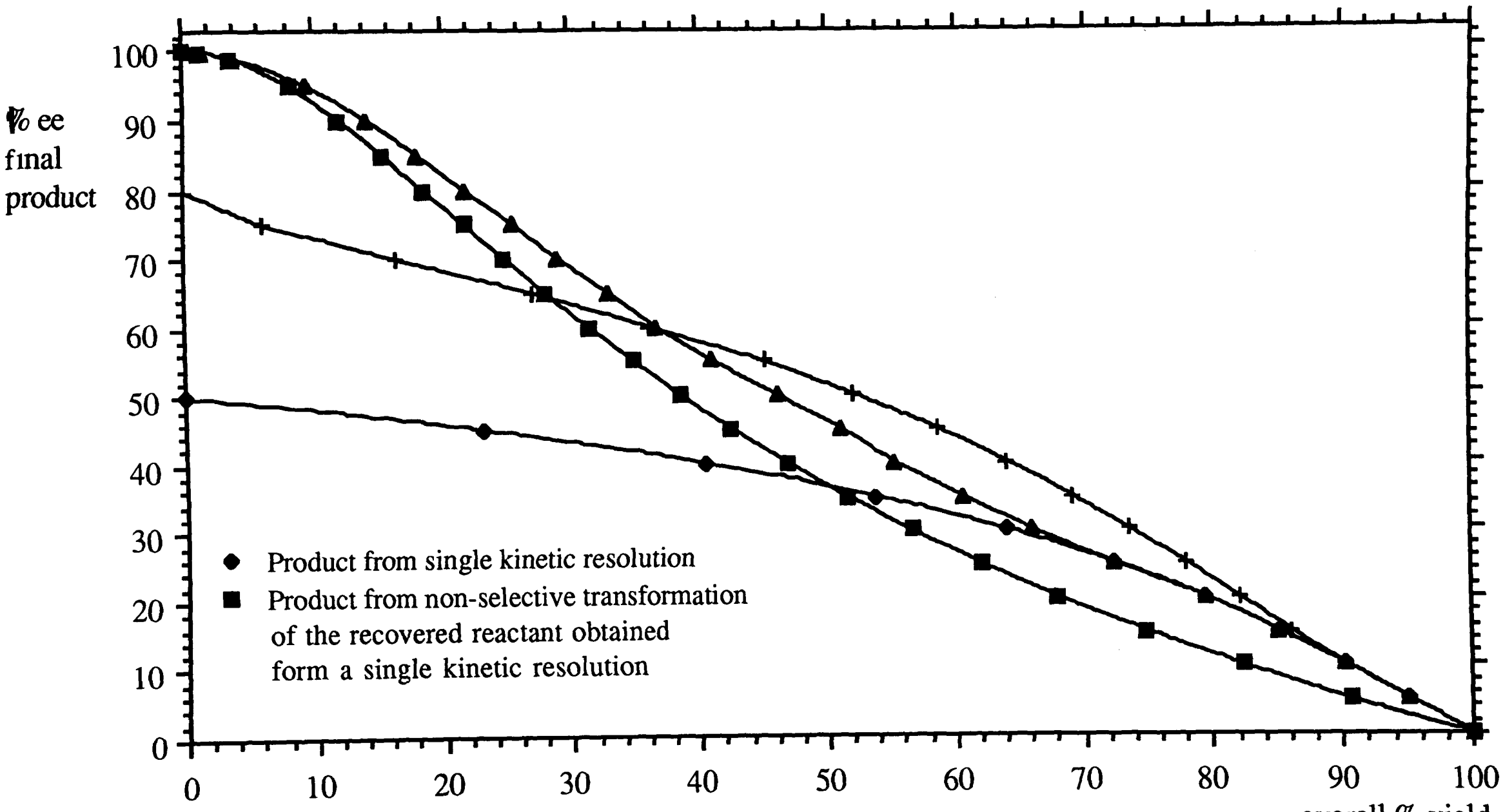
```
 %convn  %eeSM  %eeprod
   0.10   49.96   93.55
  10.00   45.20   93.16
  20.00   39.33   92.69
  30.00   31.95   92.12
  40.00   22.41   91.39
  50.00    9.57   90.43
  60.00   -8.57   89.04
  70.00  -35.79   86.77
  80.00  -76.82   81.71
  90.00  -99.87   66.65
  99.90-100.00   50.15
Initial % ee of starting material =  50
Stereoselectivity factor=  10
```

* Negative enantiomeric excesses indicate that the material is enriched in the opposite enantiomer to the original starting material.

Appendix 2

Comparison of Final Product Enantiomeric Excesses and Overall Yields obtainable by Various Kinetic Resolution Strategies.

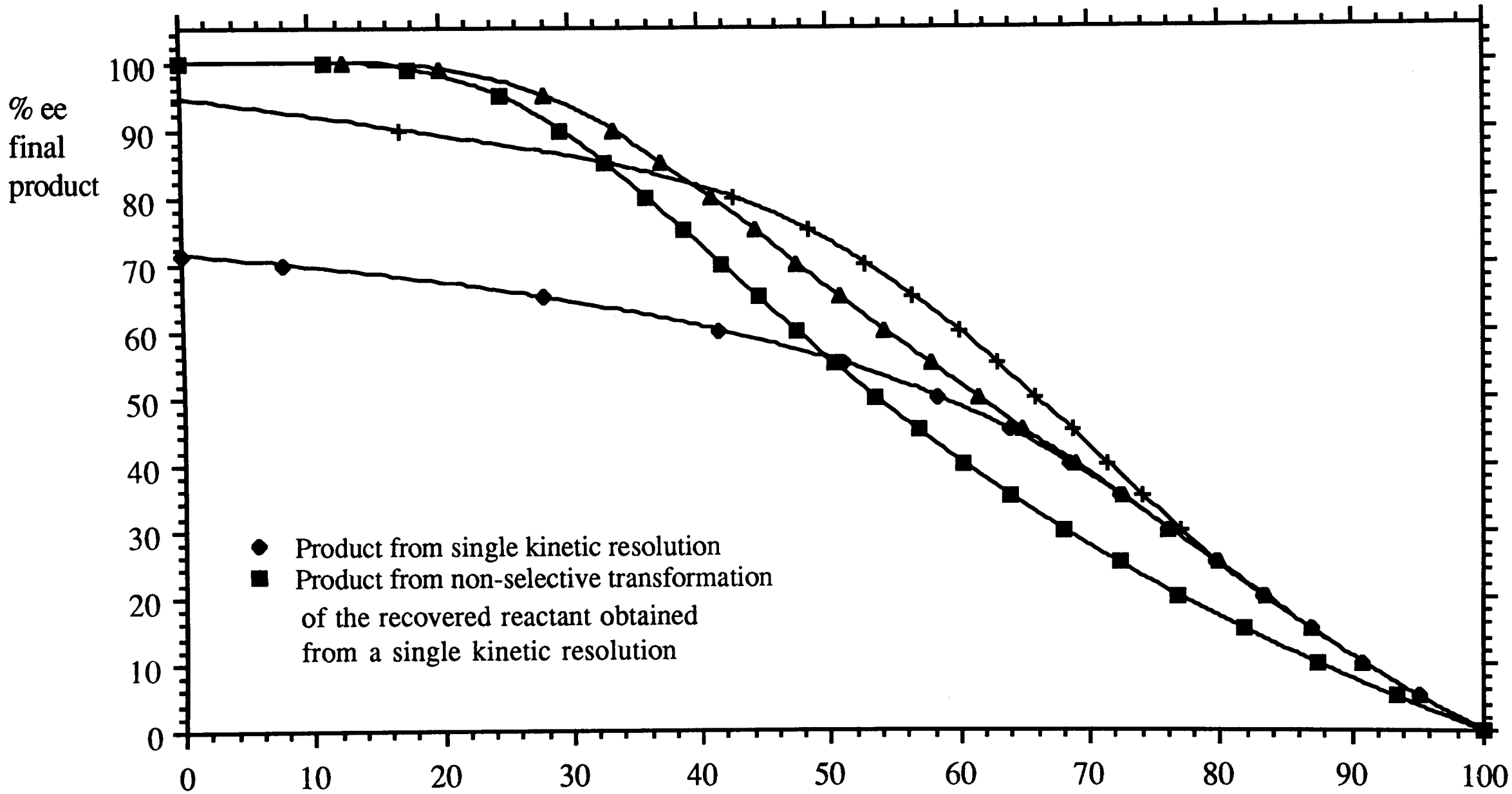
Plot of % enantiomeric excess of final product against overall % yield.
Stereoselectivity factor = 3 for both single kinetic resolution processes.
Stereoselectivity factor = 3 for each step in both double kinetic resolution processes.



▲ Product from double kinetic resolution [where the recovered reactant form the first kinetic resolution is used as starting material in the second kinetic resolution (as in Chapter 2)]

\+ Product from double kinetic resolution [where the product from the first kinetic resolution is used as starting material in the second kinetic resolution (as in Chapter 3)]

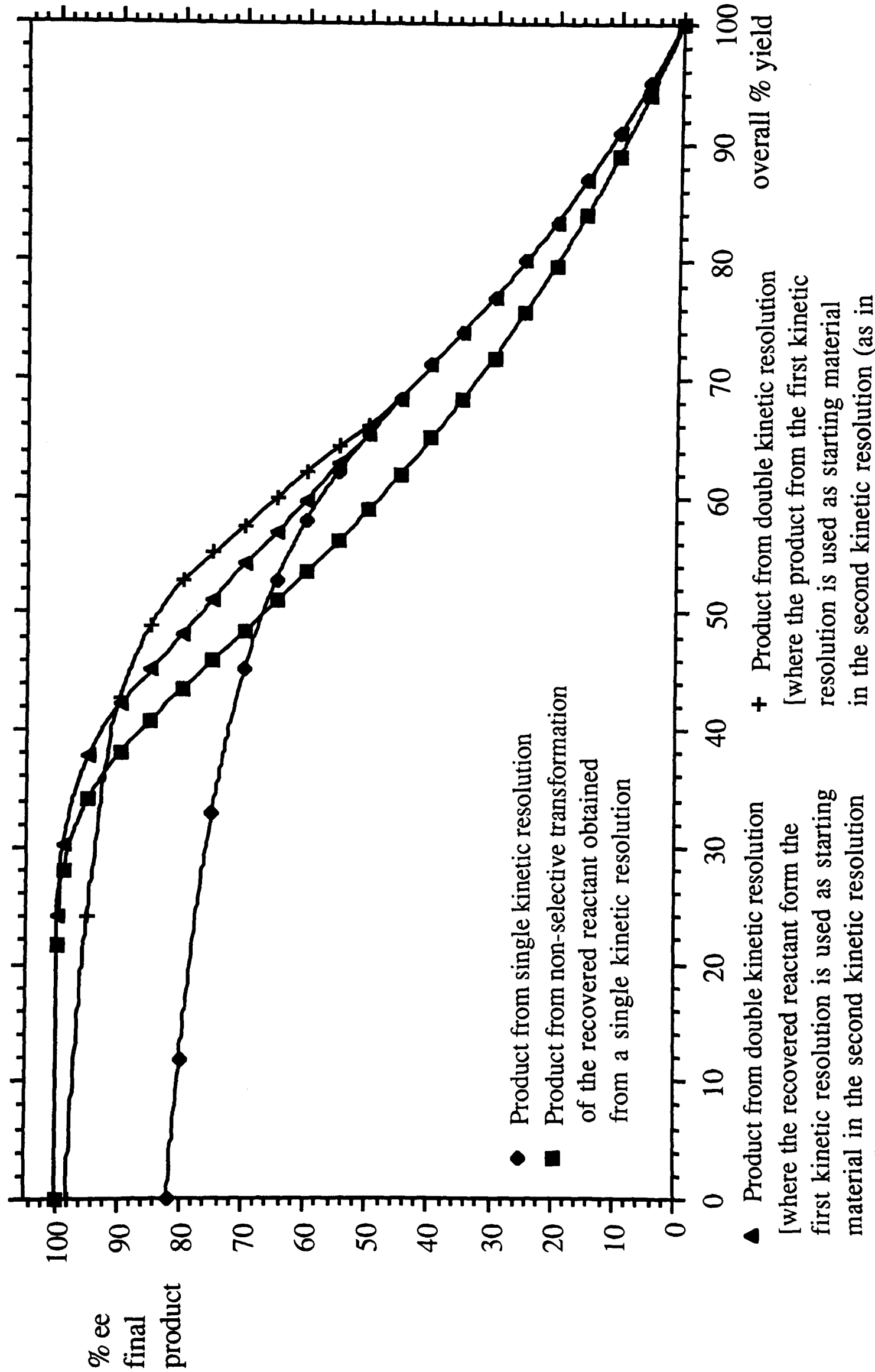
Plot of % enantiomeric excess of final product against overall % yield.
Stereoselectivity factor = 6 for both single kinetic resolution processes.
Stereoselectivity factor = 6 for each step in both double kinetic resolution processes.



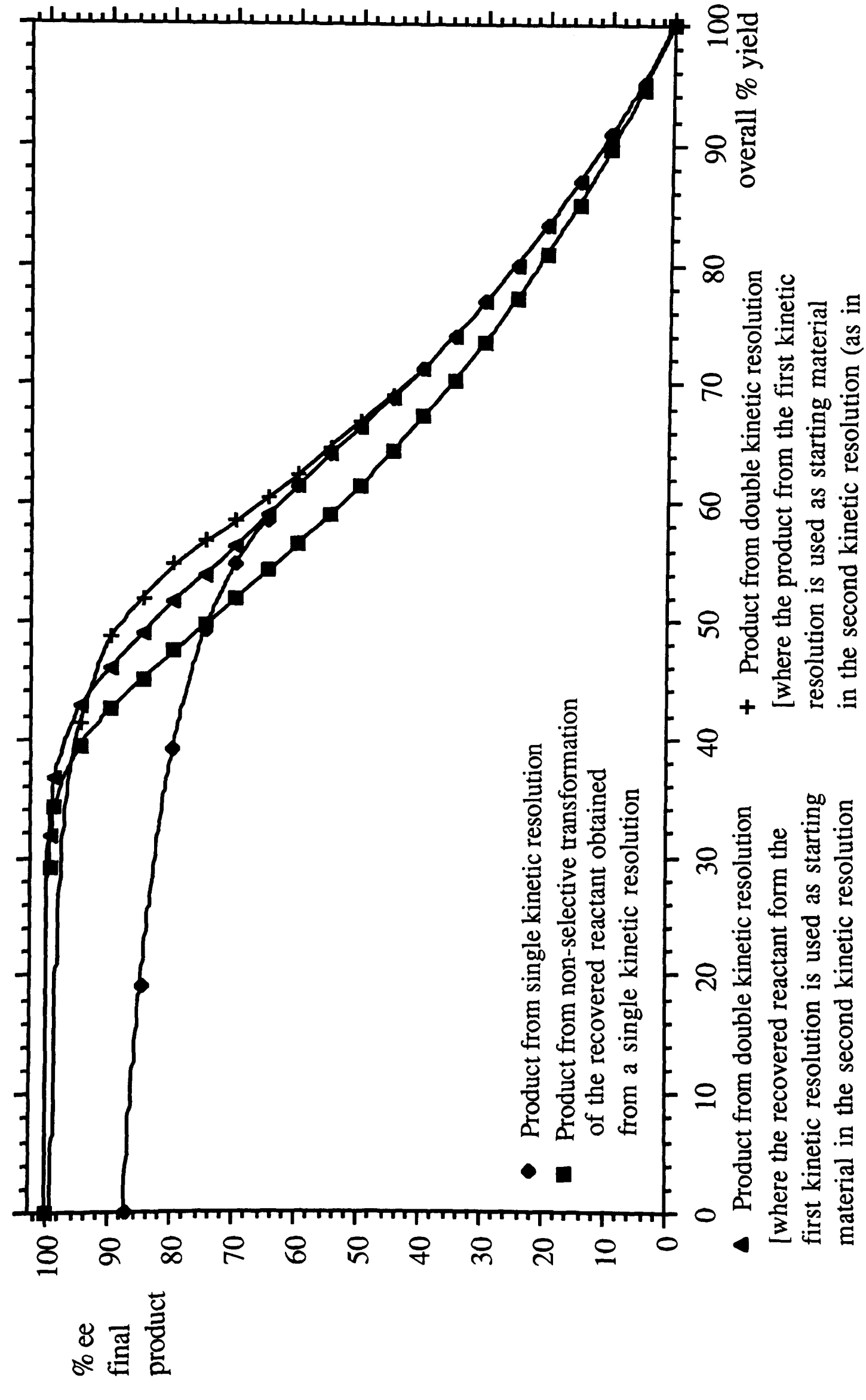
▲ Product from double kinetic resolution [where the recovered reactant form the first kinetic resolution is used as starting material in the second kinetic resolution (as in Chapter 2)]

\+ Product from double kinetic resolution [where the product from the first kinetic resolution is used as starting material in the second kinetic resolution (as in Chapter 3)]

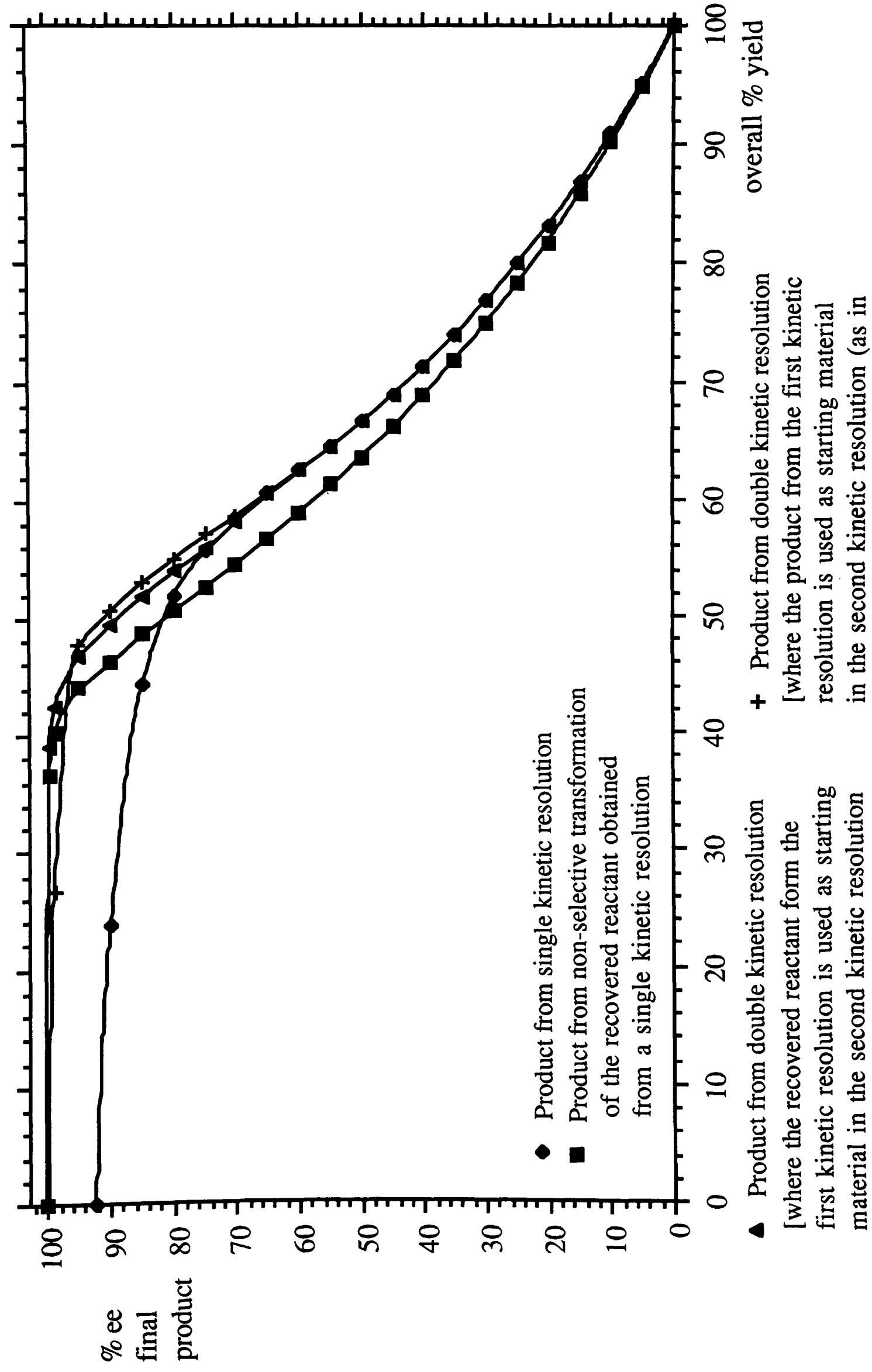
Plot of % enantiomeric excess of final product against overall % yield.
Stereoselectivity factor = 10 for both single kinetic resolution processes.
Stereoselectivity factor = 10 for each step in both double kinetic resolution processes.



Plot of % enantiomeric excess of final product against overall % yield.
Stereoselectivity factor = 15 for both single kinetic resolution processes.
Stereoselectivity factor = 15 for each step in both double kinetic resolution processes.



Plot of % enantiomeric excess of final product against overall % yield.
Stereoselectivity factor = 25 for both single kinetic resolution processes.
Stereoselectivity factor = 25 for each step in both double kinetic resolution processes.



Appendix 3

Preparation of Figure 8.

In **Figure 8**, the relationship between the % enantiomeric excess of the final product and the overall % yield for the double kinetic resolution process as described in Chapter 2 was obtained as detailed below.

The % enantiomeric excess of the recovered reactant from the first kinetic resolution (E = 6) is dependent on the conversion of the first kinetic resolution as shown in **Table I**.

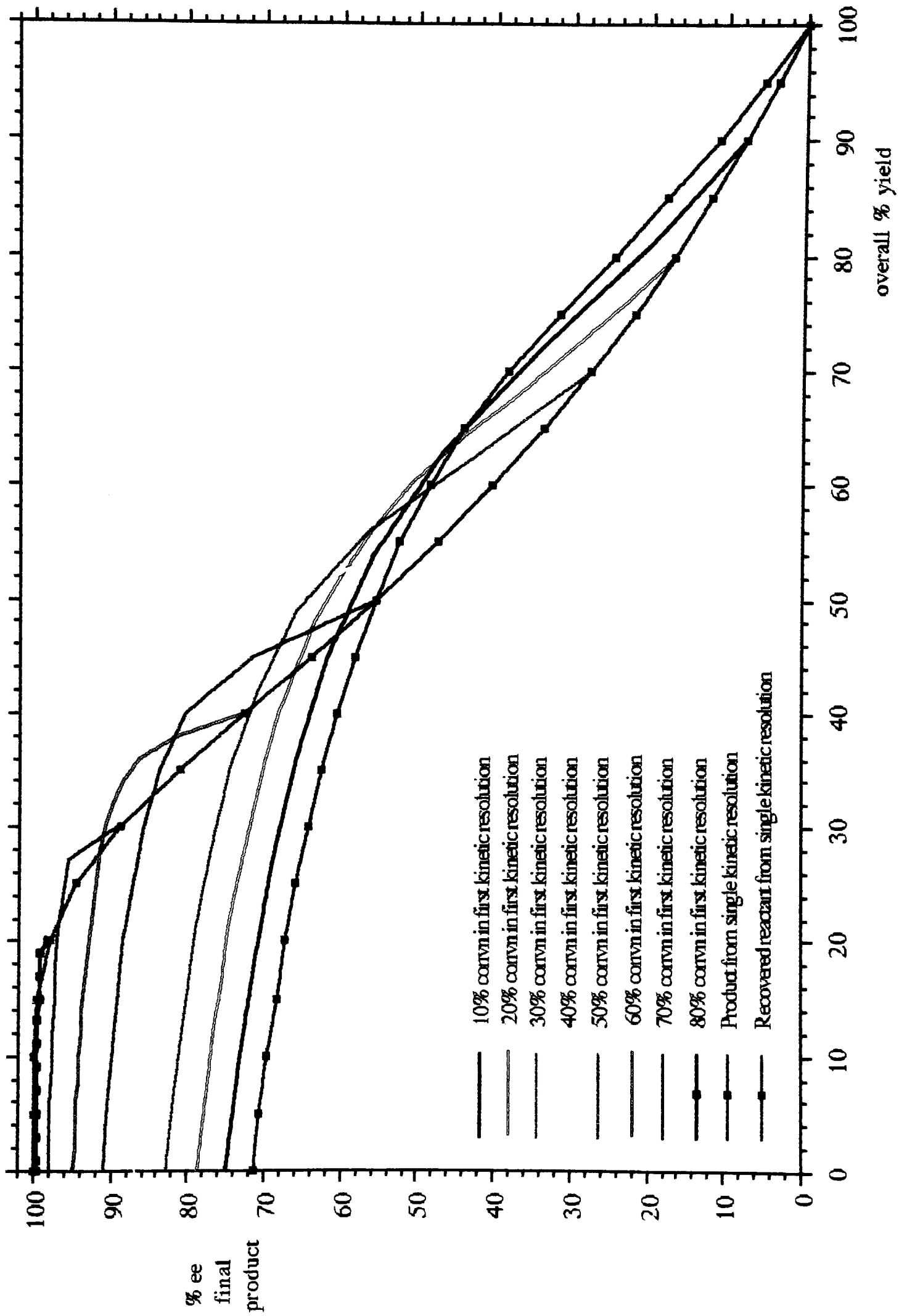
Table I

% conversion in first kinetic resolution	% ee recovered reactant	% yield of recovered reactant
10	7.7	90
20	16.8	80
30	27.6	70
40	40.4	60
50	55.7	50
60	72.8	40
70	89.0	30
80	98.1	20
90	99.9	10

If the first kinetic resolution is stopped at 40% conversion, % enantiomeric excess of the recovered reactant is 40.4%. If this material is now used as starting material in a second kinetic resolution [as described in Chapter 2 (where E = 6)], use of the computer model (Appendix 1) gives the % enantiomeric excess of the final product for any conversion. Simple calculation enables the % enantiomeric excess of the final product (from the second kinetic resolution) to be plotted against overall % yield (for both kinetic resolutions) and is shown, for this example, by the yellow line (**Figure I**). In this case maximum overall % yield is 60% (since the first kinetic resolution was run to 40% conversion). When the lines that arise from different conversions in the first kinetic resolution are also plotted, a line can be drawn that shows the maximum overall % yield obtainable using this double kinetic resolution strategy against % enantiomeric excess of the final product.

Figures 9 to **12** were prepared in a similar manner to that described above.

Figure I : % Enantiomeric excess of product from the second kinetic resolution versus overall % yield (for both kinetic resolutions).



Appendix 4

Preparation of Figure 13.

In **Figure 13**, the relationship between the % enantiomeric excess of the final product and the overall % yield for the double kinetic resolution process as described in Chapter 3 was obtained as detailed below.

The % enantiomeric excess of the product from the first kinetic resolution (E = 15) is dependent on the conversion of the first kinetic resolution as shown in **Table II**.

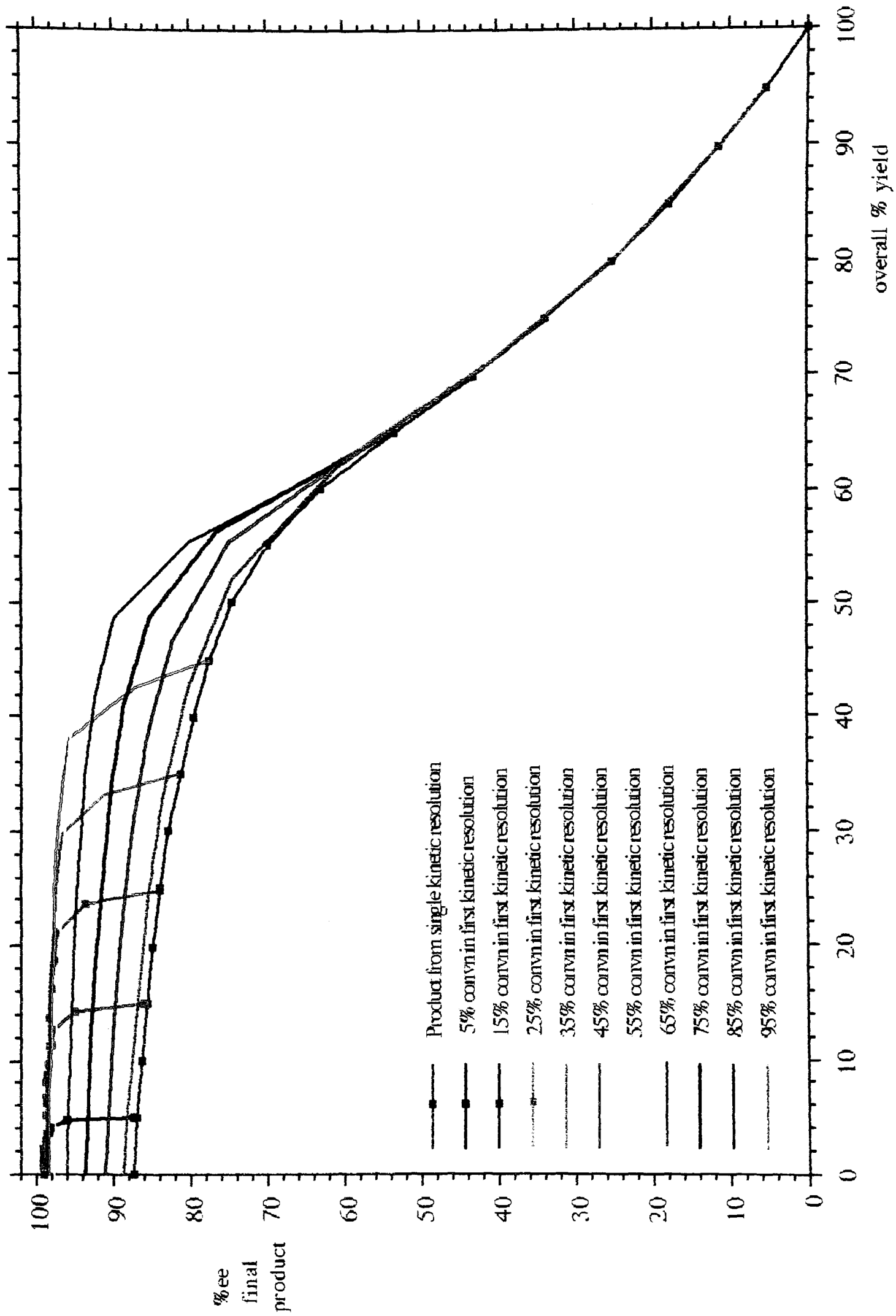
Table II

% conversion in first kinetic resolution	% ee product	% yield of product
5	87.0	5
15	85.7	15
25	83.9	25
35	81.5	35
45	77.5	45
55	69.9	55
65	53.2	65
75	33.3	75
85	17.7	85
95	5.3	95

If the first kinetic resolution is stopped at 55% conversion, % enantiomeric excess of the product is 69.9%. If this material is now used as starting material in a second kinetic resolution [as described in Chapter 3 (where E = 15)], use of the computer model (Appendix 1) gives the % enantiomeric excess of the final product for any conversion. Simple calculation enables the % enantiomeric excess of the final product (from the second kinetic resolution) to be plotted against overall % yield (for both kinetic resolutions) and is shown, for this example, by the yellow line (**Figure II**). In this case maximum overall % yield is 55% (since the first kinetic resolution was run to 55% conversion). When the lines that arise from different conversions in the first kinetic resolution are also plotted, a line can be drawn that shows the maximum overall % yield obtainable using this double kinetic resolution strategy against % enantiomeric excess of the final product.

Figures 14 to **17** were prepared in a similar manner to that described above.

Figure II : % Enantiomeric excess of product from the second kinetic resolution versus overall % yield (for both kinetic resolutions).



Appendix 5

Computer model of the reaction of lithium-(α-methylbenzyl)benzyl amide (127) with the iron crotonyl complex (129).

The diastereomeric ratio of the product (**145**) obtained from the reaction of lithium-[*(RS)*-α-methylbenzyl]benzyl amide (**129**) with *(RS)*-iron crotonyl complex (**127**) was 96 : 2 : 2 [*(RS,RS,RS)* : *(RS,RS,SR)* : *(RS,SR,SR)*]. Since mass action has no effect in a reaction between two racemic mixtures, this ratio is equivalent to the ratio of the specific rate constants for the formation of each product diastereomer. Therefore, the relative rate of reaction of the matched pair {*(R)*-**129** + *(R)*-**127** [or *(S)*-**129** + *(S)*-**127**]} and the mismatched pair {*(R)*-**129** + *(S)*-**127** [or *(S)*-**129** + *(R)*-**127**]} is 96 : 4 (or 24 : 1).

The relative rates of formation of each product diastereomer were used in a simple computer model. Given the % enantiomeric excesses of the starting materials (**127** and **129**), the computer model enables prediction of the expected % enantiomeric excesses of the recovered starting materials and the % enantiomeric and diastereomeric excesses of the product (**145**) at any conversion. The model can assume that **129** forms monomers or homochiral dimers (if homochiral dimers are assumed, then the unused part of the dimer does not return to the reaction medium).

The model was written on an Apple Macintosh Computer using Microsoft Basic. The following pages show a listing for the programme, the data input required and the form of the data output.

Listing:

```
10 INPUT "% Enantiomeric  excess of iron complex  (R>S => positive) = ";CA
20 INPUT "% Enantiomeric excess of amine  (R>S => positive) =";CB
30 INPUT "Ratio of amine to iron complex =";H
35 INPUT "Is amine monomers (1) or homochiral dimers (2)";DA
40 INPUT "Number of points to be displayed";D
50 INPUT "Relative rate of formation of RRR/SSS diastereomer =";D1
60 INPUT "Relative rate of formation of RSR/SRS diastereomer =";D2
70 INPUT "Relative rate of formation of RRS/SSR diastereomer =";D3
80 INPUT "Relative rate of formation of RSS/SRR diastereomer =";D4
85 H=H/DA
90 EA=CA/100
100 EB=CB/100
110 L=1/(D-1)
115 RC=0
116 SC=0
120 RRR=0
130 RSR=0
140 RRS=0
150 RSS=0
160 SSS=0
170 SRS=0
180 SSR=0
190 SRR=0
200 B=0
210 RA=((1+EA)/2)
220 SA=1-RA
230 RB=((1+EB)/2)*H
240 SB=H-RB
244 PRINT "            IRON COMPLEX       AMINE          RRR/SSS        RSR/SRS        RRS/SS
R      RSS/SRR
245 PRINT "  CONVN    EE    YIELD    EE    YIELD    EE    YIELD    EE    YIELD    EE    YIEL
D    EE   YIELD "
250 FOR Z=.001 TO .999 STEP .001
260 N=(RA*RB*D1)+(RA*RB*D2)+(RA*SB*D3)+(RA*SB*D4)+(SA*SB*D1)+(SA*SB*D2)+(SA*RB*D3)+(S
A*RB*D4)
270 RRRF=(.001*(RA*RB*D1))/N
280 RSRF=(.001*(RA*RB*D2))/N
290 RRSF=(.001*(RA*SB*D3))/N
300 RSSF=(.001*(RA*SB*D4))/N
310 SSSF=(.001*(SA*SB*D1))/N
320 SRSF=(.001*(SA*SB*D2))/N
330 SSRF=(.001*(SA*RB*D3))/N
340 SRRF=(.001*(SA*RB*D4))/N
350 RA=RA-RRRF-RSRF-RRSF-RSSF
360 SA=SA-SSSF-SRSF-SSRF-SRRF
370 RB=RB-RRRF-RSRF-SRRF-SSRF
380 SB=SB-SSSF-SRSF-RSSF-RRSF
385 RC=RC+((RRRF+RSRF+SRRF+SSRF)/2)
386 SC=SC+((SSSF+SRSF+RSSF+RRSF)/2)
390 RRR=RRR+RRRF
400 RSR=RSR+RSRF
410 RRS=RRS+RRSF
420 RSS=RSS+RSSF
430 SSS=SSS+SSSF
440 SRS=SRS+SRSF
450 SSR=SSR+SSRF
460 SRR=SRR+SRRF
465 C=100*Z
468 IF Z=.999 GOTO 480
470 IF Z>=B GOTO 480 ELSE 560
480 B=B+L
485 IF RA+SA=0 GOTO 495 ELSE 490
490 F1=100*((RA-SA)/(RA+SA))
495 IF RB+SB=0 GOTO 505 ELSE 500
500 F2=100*((RB-SB)/(RB+SB))
505 IF RRR+SSS=0 GOTO 515 ELSE 510
510 F3=100*((RRR-SSS)/(RRR+SSS))
515 IF RSR+SRS=0 GOTO 525 ELSE 520
520 F4=100*((RSR-SRS)/(RSR+SRS))
525 IF RRS+SSR=0 GOTO 535 ELSE 530
530 F5=100*((RRS-SSR)/(RRS+SSR))
535 IF RSS+SRR=0 GOTO 550 ELSE 540
540 F6=100*((RSS-SRR)/(RSS+SRR))
545 F7=100*((RC-SC)/(RC+SC))
546 F8=100*((((RC+SC)/(RC+SC+RB+SB))*((RC-SC)/(RC+SC)))+(((RB+SB)/(RC+SC+RB+SB))*((RB-SB)/(
RB+SB))))
550 IF DA=1 GOTO 552 ELSE 555
552 PRINT USING"####.##";C,F1,(100*(RA+SA)),F2,(100*((RB+SB)/H)),F3,(100*(RRR+SSS)),F4,(10
0*(RSR+SRS)),F5,(100*(RRS+SSR)),F6,(100*(RSS+SRR))
555 IF DA=2 GOTO 557 ELSE 560
557 PRINT USING"####.##";C,F1,(100*(RA+SA)),F8,(100*((RB+SB)/H)),F3,(100*(RRR+SSS)),F4,(10
0*(RSR+SRS)),F5,(100*(RRS+SSR)),F6,(100*(RSS+SRR))
560 NEXT Z
570 PRINT"% Enantiomeric  excess of iron complex =";CA
580 PRINT"% Enantiomeric excess of amine =";CB
600 PRINT"Relative rate of formation of RRR/SSS diastereomer =";D1
610 PRINT"Relative rate of formation of RSR/SRS diastereomer =";D2
620 PRINT"Relative rate of formation of RRS/SSR diastereomer =";D3
630 PRINT"Relative rate of formation of RSS/SRR diastereomer =";D4
640 FOR JdS = 1 TO 10000
650 NEXT JdS
660 END
```

Appendix 5

Example of Input:

```
% Enantiomeric excess of iron complex (R>S => positive) = ? 50
% Enantiomeric excess of amine (R>S => positive) =? -50
Ratio of amine to iron complex =? 1
Is amine monomers (1) or homochiral dimers (2)? 1
Number of points to be displayed? 21
Relative rate of formation of RRR/SSS diastereomer =? 96
Relative rate of formation of RSR/SRS diastereomer =? 0
Relative rate of formation of RRS/SSR diastereomer =? 2
Relative rate of formation of RSS/SRR diastereomer =? 2
```

Example of Output:

	IRON COMPLEX		AMINE		RRR/SSS		RSR/SRS		RRS/SSR		RSS/SRR	
CONVN	EE	YIELD	EE	YIELD	EE	YIELD	EE	YIELD	EE	YIELD	EE	YIELD
0.10	50.04	99.90	-50.04	99.90	0.00	0.09	0.00	0.00	80.00	0.00	80.00	0.00
5.00	52.35	95.00	-52.35	95.00	0.00	4.67	0.00	0.00	81.07	0.17	81.07	0.17
10.00	54.93	90.00	-54.93	90.00	0.00	9.32	0.00	0.00	82.20	0.34	82.20	0.34
15.00	57.79	85.00	-57.79	85.00	0.00	13.95	0.00	0.00	83.37	0.53	83.37	0.53
20.00	60.96	80.00	-60.96	80.00	0.00	18.55	0.00	0.00	84.58	0.73	84.58	0.73
25.00	64.50	75.00	-64.50	75.00	0.00	23.11	0.00	0.00	85.83	0.95	85.83	0.95
30.00	68.47	70.00	-68.47	70.00	0.00	27.62	0.00	0.00	87.12	1.19	87.12	1.19
35.00	72.93	65.00	-72.93	65.00	0.00	32.07	0.00	0.00	88.47	1.47	88.47	1.47
40.00	77.96	60.00	-77.96	60.00	0.00	36.41	0.00	0.00	89.88	1.79	89.88	1.79
45.00	83.57	55.00	-83.57	55.00	0.00	40.58	0.00	0.00	91.35	2.21	91.35	2.21
50.00	89.68	50.00	-89.68	50.00	0.00	44.45	0.00	0.00	92.91	2.78	92.91	2.78
55.00	95.63	45.00	-95.63	45.00	0.00	47.63	0.00	0.00	94.59	3.68	94.59	3.68
60.00	99.29	40.00	-99.29	40.00	0.00	49.32	0.00	0.00	96.26	5.34	96.26	5.34
65.00	99.96	35.00	-99.96	35.00	0.00	49.59	0.00	0.00	97.41	7.71	97.41	7.71
70.00	100.00	30.00	-100.00	30.00	0.00	49.60	0.00	0.00	98.04	10.20	98.04	10.20
75.00	100.00	25.00	-100.00	25.00	0.00	49.60	0.00	0.00	98.43	12.70	98.43	12.70
80.00	100.00	20.00	-100.00	20.00	0.00	49.60	0.00	0.00	98.68	15.20	98.68	15.20
85.00	100.00	15.00	-100.00	15.00	0.00	49.60	0.00	0.00	98.87	17.70	98.87	17.70
90.00	100.00	10.00	-100.00	10.00	0.00	49.60	0.00	0.00	99.01	20.20	99.01	20.20
95.00	100.00	5.00	-100.00	5.00	0.00	49.60	0.00	0.00	99.12	22.70	99.12	22.70
99.90	100.00	0.10	-100.00	0.10	0.00	49.60	0.00	0.00	99.21	25.15	99.21	25.15