Tetrahedron: Asymmetry Vol. 2, No. 8, pp. 733-750, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

TETRAHEDRON: ASYMMETRY REPORT NUMBER 5

Pseudomonas fluorescens Lipase in Asymmetric Synthesis

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(*Received* 6 *May* 1991)

CONTENTS

1. Introduction

The chemo-enzymatic approach to asymmetric synthesis is finding increasing acceptance in synthetic strategies and the use of an enzyme as a routine chiral catalyst for asymmetric synthesis is now well documented.[1] Lipase is an enzyme which releases fatty acids nonregiospecifically or regiospecifically from the outer 1- and 3-positions of acylglycerols.[2] Lipase is capable of catalysing asymmetric hydrolysis[3] and esterification[4] of a wide range of substrates. This ability has attracted enhanced attention of synthetic chemists because it requires no added cofactors and is readily available and easily handed. In order to make lipase become a general and practical reagent for asymmetric synthesis, there is an urgent need to investigate substrate specificities systematically with enzymes so that the right enzyme for a given substrate can be selected with a much greater degree of confidence.

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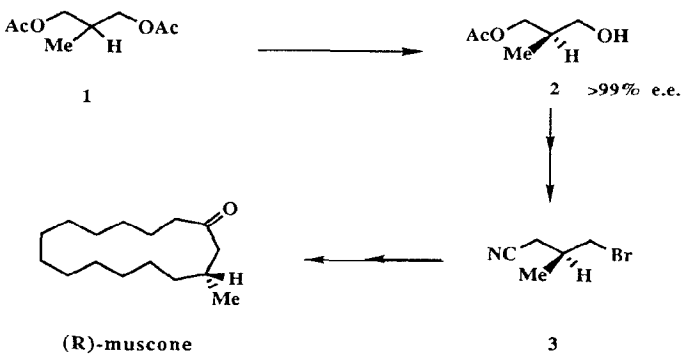
At present, there have been no comprehensive reviews of lipase in asymmetric synthesis although some separated reviews of enzymes in organic synthesis have appeared.[1] This review deals with lipase-catalysed asymmetric reactions, which include hydrolysis and esterification as well lactonization. Emphasis has been placed in this review on PFL (Pseudomonas fluorescens lipase)[5] as a synthetically useful chiral catalyst which synthetic chemists have already used in the asymmetric syntheses of both natural products and biologically active compounds.

2. Asymmetric hydrolysis

2.1 Prochiral diesters as substrates

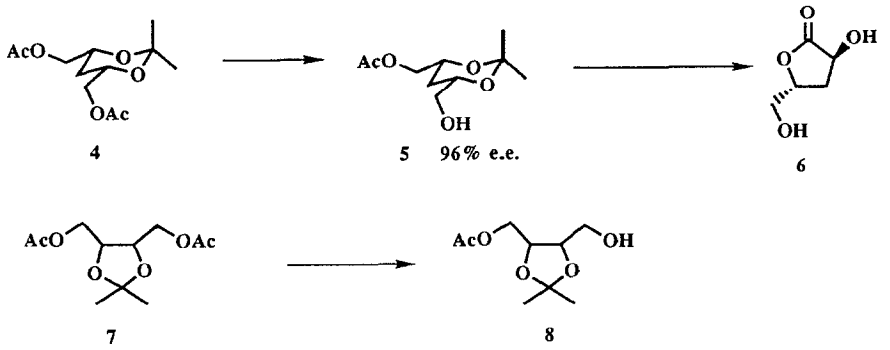
One of the biotransformations that is difficult to emulate chemically was demonstrated by lipase catalysed asymmetric hydrolysis of prochiral diacetates. Differentiation of the two enantiotopic groups in prochiral diacetates like (1) would in fact lead to bifunctional chiral molecules (2), which could be transformed into both enantiomeric series by selective functional group manipulation of (2). The resulting bifunctional chiral molecules can permit chain elongation at either end of the molecule. This prochiral trick has already been adopted to prepare chiral compounds efficiently.

An example was demonstrated by the PFL-catalysed asymmetric hydrolysis of prochiral 2-methyl propane diacetate (1), which occurred with Pro-R selectivity to offer the optically pure mono acetate (+)-(2). Chiral compounds like (2) has proven to be exceptionally valuable in the synthesis of polyener antibiotics.[6] After one carbon elongation, (2) was converted to a bifunctional chiral C_5 isoprenoid (3), a common unit which is found in tocopherol, phylloquinones phytol and insect pheromones.[7] More interestingly, (3) was introduced onto a 15-membered ring for a facile synthesis of (-)-muscone [8] by a combination of a three-carbon ring expansion (Scheme 1).



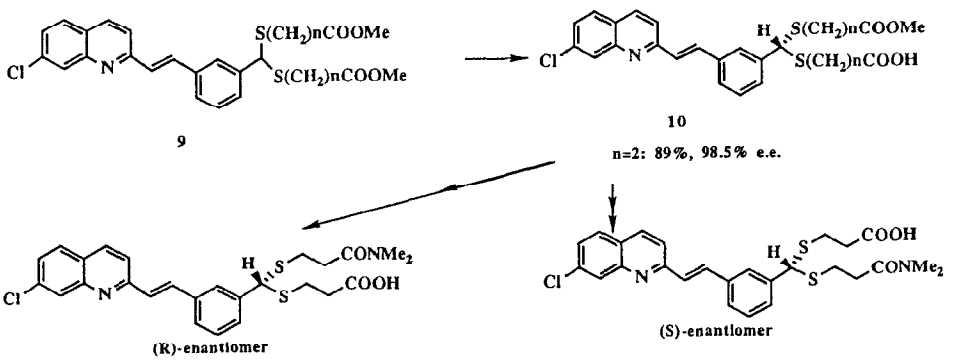
Scheme 1

A conformationally rigid compound (4) has been designed and subjected to hydrolysis with PFL to afford the (-)-monoacetate (5) with a 96% e.e. and 79% chemical yield.[9] This procedure provides a practical and efficient synthesis of chiral 1,3-syn-diols.[10] For example, oxidation of (5) followed by hydrolysis and subsequent lactonization afforded one of four possible stereoisomers of the hunger modulator compound (6).[11] In contrast, hydrolysis of the five-membered diacetate (7) led to the racemic monoacetate (8), which may be due to the flexibility of its conformation (Scheme 2).



Scheme 2

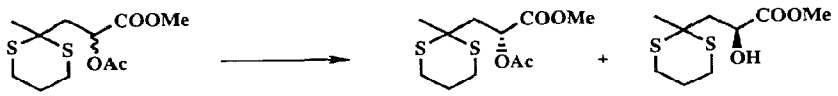
PFL is capable of selectively hydrolysing prochiral diesters such as (9) with distances of up to five bonds between the prochiral center and the ester carbonyl.[12] Chemical yields and e.e.'s were better with the substrate having four bonds between the prochiral center and ester carbonyl than with the three bond or five bond analogues. Compound (10) was obtained in 89% yield with 98.5% e.e.. The chiral ester-acid was treated with Weinreb's reagent to give R-enantiomer of the product, while the S-enantiomer could also be prepared by an alternative chemical elaboration. Both enantiomers are potent LTD4 antogonists (Scheme 3).



Scheme 3

2.2 Acyclic racemates as substrates

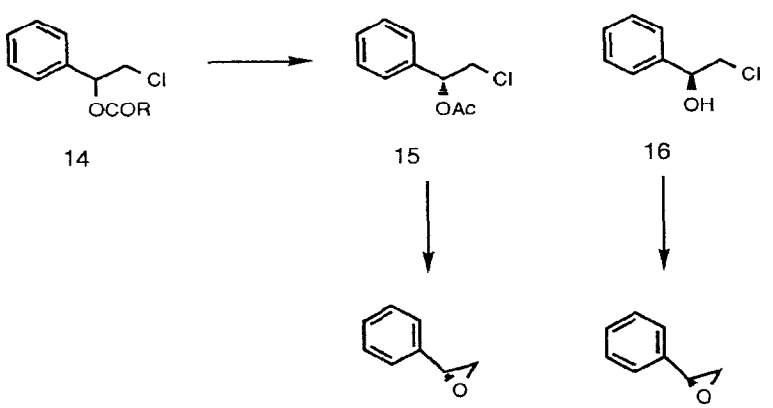
The ideal resolution of (±)-1-acetoxy esters such as (11) was achieved using PFL-catalysed hydrolysis. Both acetate (12) and resulting alcohol (13) were obtained in high enantioselectivity. The chiral alcohol is a precursor for the synthesis of PAF[13](Scheme 4).



11 12 97% e.e. 13 96% e.e.

Scheme 4

Chiral 2-halo-1-hydroxy-phenylethanes are versatile intermediates for the synthesis of natural compounds and new drugs. It was shown that (±)-2-chloro-1-hydroxy-phenylethane esters (14) are also good substrates of PFL.[14] PFL preferentially hydrolyses its (S)-acetate to give optically pure (-)-R acetate (15) (24%) and (+)-S alcohol (16) (29%) (Scheme 5). The length of acyl residues from acetyl to octanoyl in the substrates did not influence the enantioselectivity. Both enantiomers of optically active styrene oxides were synthesized in this way from the enzymatic products.

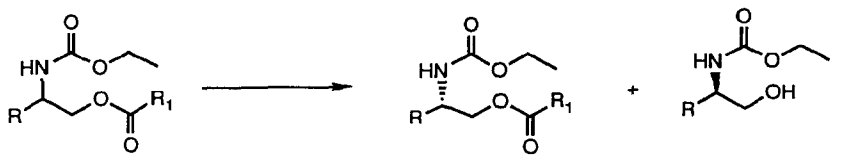


14 15 16

Scheme 5

Resolutions of 2-amino-1-alcohols (18) were readily accomplished using PFL-catalysed hydrolysis of derived esters thus providing chiral 2-amino 1-alcohols (18),[15] which are potentially

important both as chiral building blocks and as products of pharmaceutical interest (Scheme 6). In this hydrolysis, protection of the amino group is necessary to achieve the optical resolution. Recourse to alkoxycarbonyl group for protection of the amine was made since it can be selectively introduced and was easily removed at the end of the reaction.

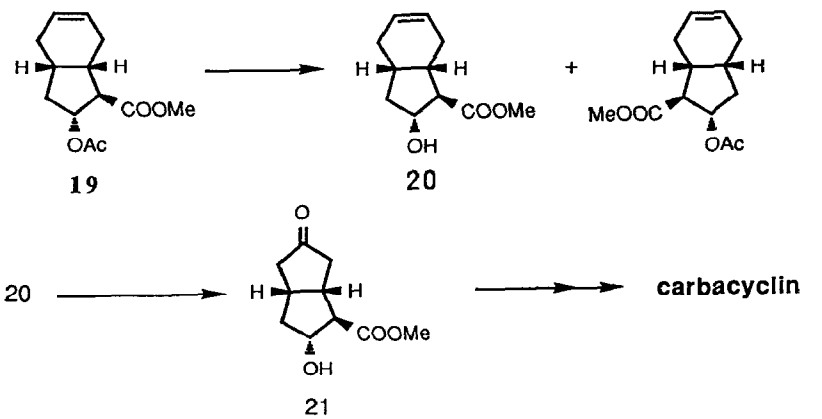


17 18

Scheme 6

2.3 Cyclic racemates as substrates

Resolution of (19) via enantioselective hydrolysis by PFL of its ester was carried out. Screening of a series of enzymes showed that PFL provided best results in terms of both chemical yield and optical yield. Chiral alcohol (20), obtained in this way has been transformed to (21) using a ring contraction as a key step for synthesis of carbacyclin[16] (Scheme 7).

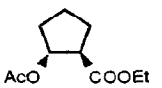
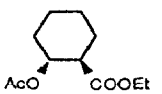
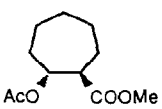
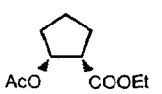
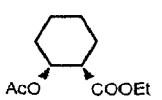
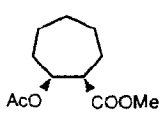
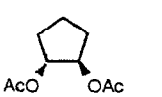
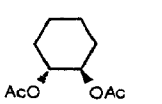
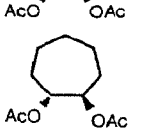


19 20 21

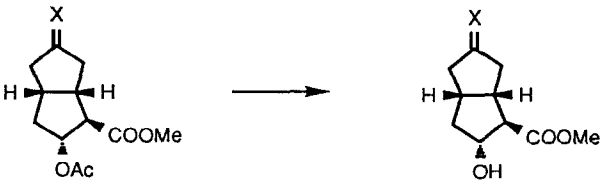
Scheme 7

In connection with this work, PFL-catalysed hydrolysis of a series of cyclic 2-alkoxycarbonyl-alkylane-1-yl acetates was reported [17,18](Table 1). It was found that invariably acetates possessing an R-configurated alcohol center were preferentially cleaved by PFL independant of the stereochemistry of 2-alkoxycarbonyl. In addition, the change of ring size exerts no influence on the stereochemical outcome of the resulting carbinols.

Table 1

	hydrolysed product		recovered acetate	
	CY(%)	e.e.%	CY(%)	e.e.%
	30	>99 (1R,2S)	65	30
	41	>99(1R,2S)	59	55
	45	>99(1R,2S)	50	78
	42	>99(1R,2R)	50	90
	32	>99(1R,2R)	63	70
	38	>99(1R,2R)	58	68
	43	>99(1R,2S)	42	95
	32	>99(1R,2S)	51	48
	30	>99(1R,2S)	64	45

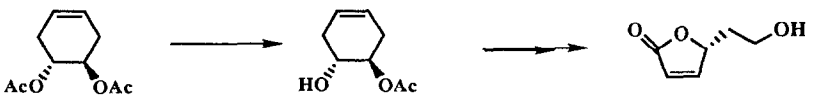
In the hydrolysis of bicyclic acetates,[17] it has been described that the PFL substrate (22), a key intermediate for synthesis of carbacyclin, was of a very low reactivity and the protected derivative (23) was almost resistant to PFL. By contrast, the hydrolysis of modified acetate (24) with a more hydrophobic character showed a marked enhancement with respect to both the enantiomeric excess (>99%) and the hydrolysis rate (4h). This study to modify the substituent pattern of the substrate for enhancement of e.e. represents a potential utilization of enzyme in the asymmetric synthesis (Scheme 8).



22 X=O
23 X=OCH_2CH_2O
24 X=CH_2

Scheme 8

Similarly, trans-1,2-diacetoxy cycloalkanes ,[17,18] were also efficiently resolved into their corresponding enantiomers (Table 1). Trans 1,2-diacetoxy cyclohexene (25),[19] was hydrolysed in a highly enantioselective fashion to yield (-)-(26) with 99% e.e.. Chiral monoacetate (26) has been used as a starting material to prepare the γ-hydroxyethyl-$\alpha\beta$-unsaturated γ-lactone (27), a useful intermediate for the synthesis of eldanolide (Scheme 9).



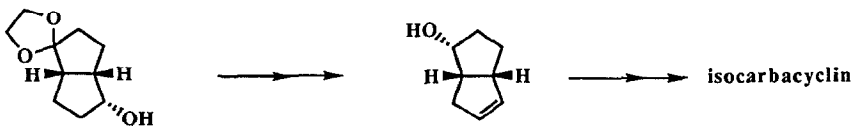
25 26 >99% e.e. 27

Scheme 9

Bicyclic acetates can be hydrolysed with PFL. PFL-catalysed hydrolysis of (28) occurred with R-specificity to produce the optically pure alcohol (29).[20] The rate of hydrolysis increased with the rate of hydrophobic property of the substrates. Corresponding exo-acetates are not substrates for PFL and can be recovered under the same condition. Optically pure alcohol (29) was converted in a stereocontrolled manner to a precursor (30) for the synthesis of isocarbacyclin (Scheme 10).

28 99% e.e.

X= O, OCH_2CH_2O, CH_2



29 30

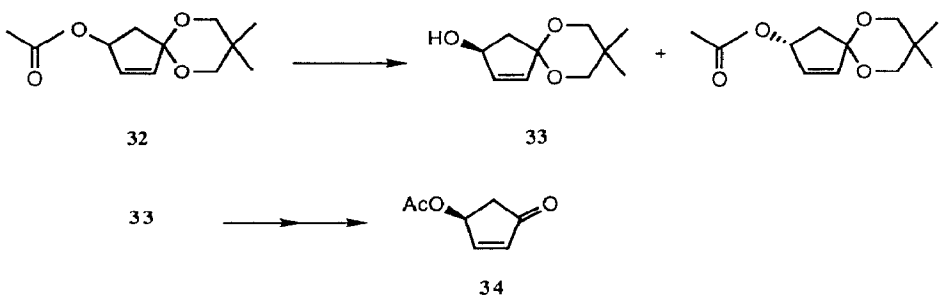
Scheme 10

Norbornane-type esters (3 1) are also found to be hydrolysed with PFL to give the R-(+) alcohol in 97% e.e., while under the same condition, the substrates with an epoxide or acetonide function can not be hydrolysed, which implies that a hydrophobic substrate is a requirement. Again, the R-enantiomers are preferentially hydrolysed. The chiral bicyclic alcohols have proved to be useful synthons for syntheses of prostaglandins [21] (Scheme 11).

31 >97% e.e.

Scheme 11

The versatility of PFL is further demonstrated by its role in the preparation of cyclopentanoid natural products. The racemic ketal of 4-acetoxycyclopent-2-en-1-one (3 2) was efficiently resolved into (S)-alcohol (3 3) and (R)-acetate with PFL [22](Scheme 12). Chiral alcohol (3 3) was easily converted into optically pure 4-(S)-acetoxycyclopentenone (3 4) without any racemization.

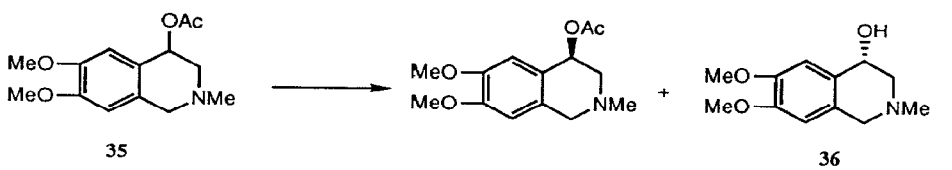


32 33

33 34

Scheme 12

The hydrolysis reaction is usually undertaken in water solution. However, if an acetate is susceptible to solvolysis, the lipase-catalysed hydrolysis might result in nonselectivity as reported in the hydrolysis of tetrahydroisoquinolines. This problem has been solved by using PFL immobilized on celite in organic solvents. Hydrolysis of (±)-4-acetoxy-1,2,3,4-tetrahydro-6,7-dimethoxy-2- methylisoquinoline (3 5) with this enzyme in isooctane afforded alcohol (3 6) in 81 % e.e. [23](Scheme 13).



35 36

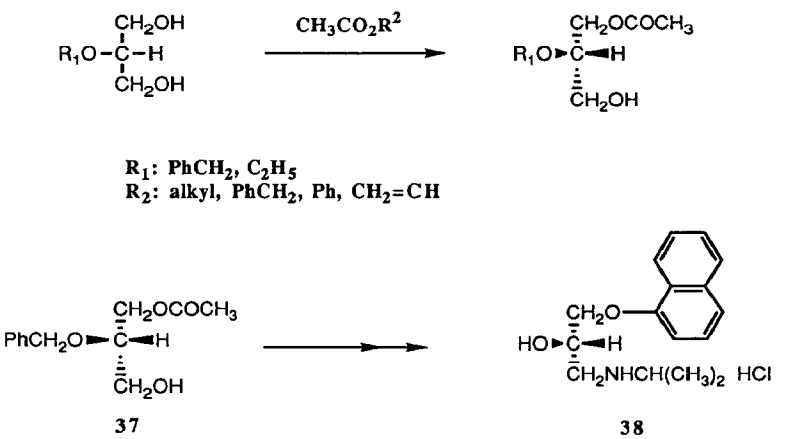
Scheme 13

3. Asymmetric esterifications

In addition to hydrolysis, lipase should also be able to catalyse different reactions where compounds other than water serve as nucleophiles (eg. alcohol, amine, thiols).[24] Both enzymatic esterification and hydrolysis occur via a common acyl-enzyme intermediate. The use of lipases as catalysts for esterification reactions has attracted considerable attention recently. Because of their relatively high stability in organic media, they can also be used in organic solvents for certain types of transformations which are difficult to do in water. These alternative reactions are applicable to a wide variety of water-insoluble substrates and have the advantage of greatly simplifying product recovery. It should be pointed out that not all of the lipases can catalyse esterification in organic solvents with high stereoselectivity. Extensive examination reveals that PFL is a good catalyst to meet the needs of both stereoselectivity and activity.

3.1 Enol esters as acylating agents

Esterification of 2-O-benzyl glycerol with various acetates was successfully undertaken using PFL. Vinyl and phenyl acetates were found to be effective to afford (S)-2-O-benzylglycerol-1 acetate (37) in high optical yield, which was converted into optically pure (S)-propranolol hydrochloride, an aryloxypropylamine type β-blocke (38)[25] (Scheme 14).

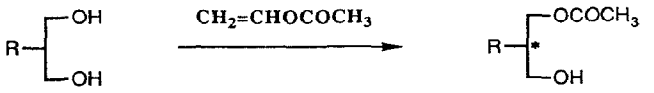


37 38

Scheme 14

Chiral 2-substituted propanediols were obtained by PFL catalysed esterification of prochiral diols. The influence of 2-substitution pattern on the optical yield was also reported. 2-benzyl and 2-(1-naphthylmethyl) propanediol gave the corresponding monoester in high chemical as well as optical, yield. Similar transesterification of 2,4-dimethyl-1,5-pentanol with vinyl acetate as an acylating agent led to the (2R,4S) enantiomer in good optical yield. Chemoselective elaboration of

(39) allowed the preparation of (S)-3-isopropylsulfonyl-2-benzylpropionic acid (40), a key intermediate for the synthesis of a renin inhibitor [26](Scheme 15).

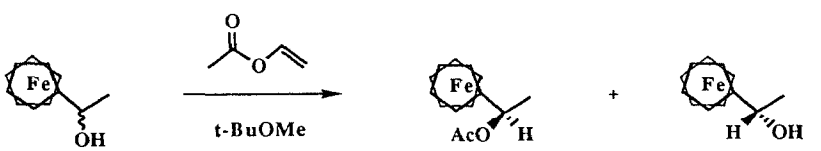


R: CH_3, $(CH_3)_2CH$, $CH_2{=}CHCH_2$, $C_6H_5CH_2$, $C_{10}H_7CH_2$

39 40

Scheme 15

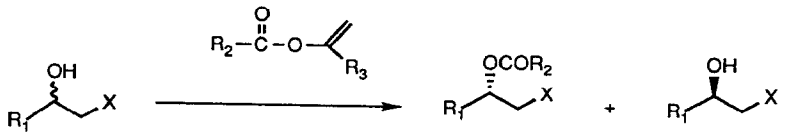
PFL found its use in the synthesis of chiral ferrocenylethanol. The design of the substrate was based on an active site working hypothesis by which R-enantioselectivity can be predicted. PFL-catalysed esterification of 1-ferrocenylethanol (41) in t-BuOMe provided the R-acetate (42) (96% e.e.) and S-alcohol (92% e.e.).[27]Both chiral compounds can be elaborated to the optically active ferrocenyl bis-phosphines such as BPPFA and BPPF, highly useful ligands for homogeneous asymmetric catalysis. This is a good example which demonstrates the usefulness of biocatalysis in organometallic chemistry (Scheme 16).



41 42 96% e.e. 92% e.e.

Scheme 16

PFL was reported to be effective in the transesterification of the racemic 2-halo-1-arylethanols. In each case, the lipase was found to catalyse the acylation of the S-isomer of 2-halo-1-arylethanol exclusively, indepentant of the structure of both R_1 and enol esters used[28] (Scheme 17).



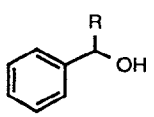
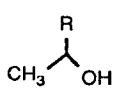
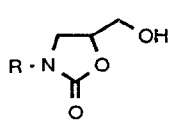
R_1: aryl
X: Br, Cl
R_2: CH_3, n-C_3H_7, n-C_7H_{15}
R_3: H, CH_3

Scheme 17

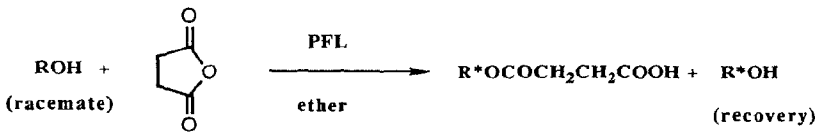
3.2 Anhydrides as acylating agents

The use of enol-esters for the transesterification has the disadvantage of side reactions caused by decomposition of enol alcohols to aldehydes. This problem can be overcome by using anhydrides as acylating agents. Such an approach involves no formation of water or alcohol thus shifting the reaction toward the product.[29] A number of primary and secondary alcohols have been obtained in high optical purity by acylation of racemates using PFL adsorbed on celite (Table 2). Among the tested anhydrides (acetic, propionic, butyric), propionic anhydride gave the best results in all the cases.

Table 2

substrate		recovered alcohol		produced ester	
		CY(%)	e.e.%	CY(%)	e.e.%
	1: R=Me	46	94(S)	40	>95
	2: R=Et	39	87(S)	34	>95
	3: R=$PhCH_2$	43	92(S)	39	>95
	4: R=n-C_6H_{13}	35	54(S)	33	61
	5: R=n-$C_{10}H_{21}$	35	63(S)	41	76
	6: R=$C(CH_3)_3$	45	>95(S)	42	>95
	7: R=$CH(CH_3)_2$	41	>95(S)	40	>95

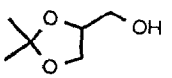
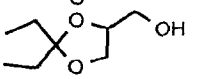
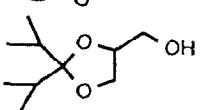
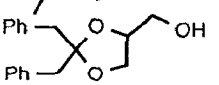
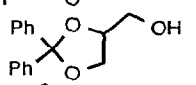
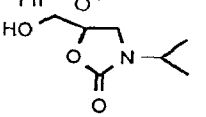
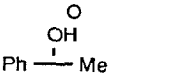
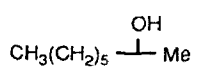
Lipase-catalysed esterification of a series of racemic alcohols with succinic anhydride proceeded enantioselectively to afford succinic acid monoesters and optically active alcohols (Scheme 18).[30] The optical resolution of racemic alcohols including glycerol derivatives was realized in this way (Table 3). Substituents at the 2-position of 1,3-dioxolane-4-methanols were found to affect the enantioselectivity of the resulting product. The diisopropyl group gave a good result with the use of PFL.



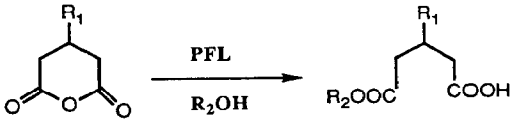
ROH: glycerol derivative, secondary alcohol

Scheme 18

Table 3

Substrate	produced acetate		recovered alcohol	
	CY (%)	OY (%e.e.)	CY (%)	OY (%e.e.)
	40	60 (S)	40	61 (R)
	40	61 (S)	47	37 (R)
	47	81 (S)	46	80 (R)
	45	67 (S)	42	60 (R)
	55	30 (S)	40	41 (R)
	46	75 (R)	38	98 (S)
	45	99 (R)	41	97 (S)
	45	82 (R)	43	78 (S)

PFL can discriminate between two enantiotopic carbonyl groups. This was illustrated by esterification of 3-substituted glutaric anhydrides with 1-butanol in organic solvents thus providing the R-half esters with 60-91% e.e..[31] The examination of the effect of solvent on the e.e. showed that diisopropyl ether was the most appropriate. The half ester of 3-methyl glutaric anhydride with 1-butanol in diisopropyl ether with 91% e.e. was obtained in 74% chemical yield (Scheme 19).

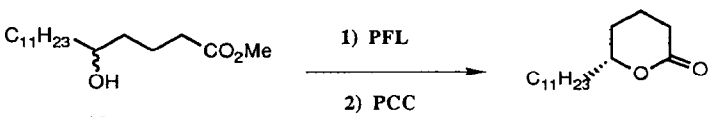


R1: methyl, ethyl, propyl, isopropyl
R2: methanol, 1-butanol, 2-propanol

Scheme 19

4. Asymmetric lactonization

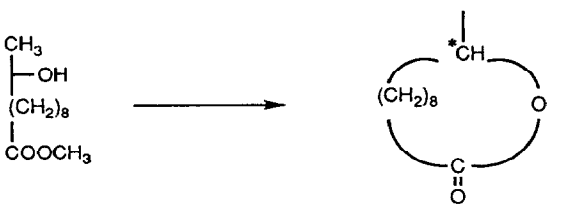
PFL catalysed enantioselective lactonization can be accomplished in an organic solvent. Subjection of racemic hydroxy ester (43) to immobilised PFL in isooctane followed by direct oxidation with PCC led to the formation of (R)-5-hexadecanolide (44) (35% yield, 70% e.e.), a pheromone of the oriental hornet [32] (Scheme 20).



43 **44**

Scheme 20

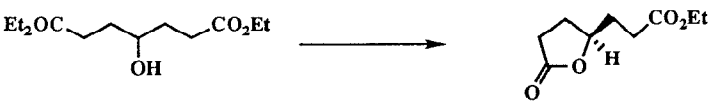
Also, a stereoselective intramolecular transesterification of racemic methyl 10-hydroxyundecanoate (45) was catalysed by PFL to give the chiral macrocyclic lactone (46).[33] This chemo-enzymatic approach to asymmetric lactone synthesis has significant advantages over conventional chemical synthesis of lactones (Scheme 21).



45 **46**

Scheme 21

Asymmetric lactonization of γ-hydroxy diesters (47) was described utilizing the prochiral stereoselectivity of PFL in organic solvents. At 100% conversion, (R)-lactone (48) was obtained with 32% e.e. [34](Scheme 22).

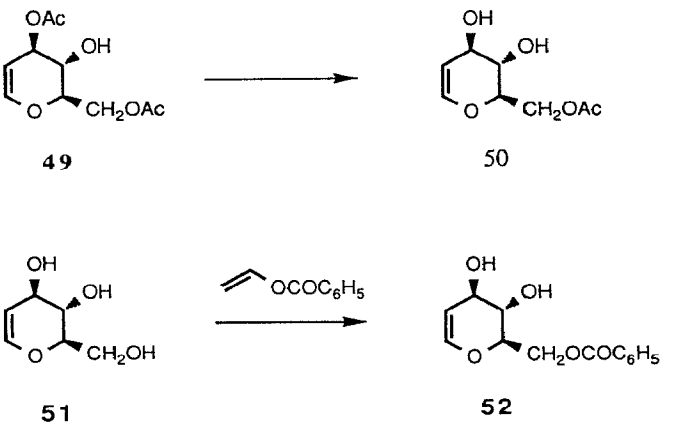


47 48

Scheme 22

5 Miscellaneous

The direct chemical transformation of glycals, which are versatile chiral building blocks, at a free hydroxy group usually requires tedious multistep protection and deprotection procedures. PFL was used to catalyse an acetyl transfer reaction regioselectively, which provides an alternative to selectively protected glycals[35] (Scheme 23). PFL-catalysed ester cleavage of (49) in weakly buffered solution afforded 4,6-di-O-acetyl-D-glucal (50). In contrast, PFL was shown to be suitable for the selective benzoylation of the 6-hydroxy group of glycal (51) to give (52).

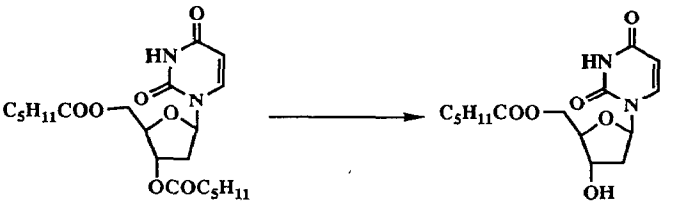


49 50

51 52

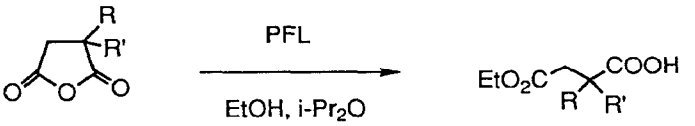
Scheme 23

Similarly, regioselective deprotection at the secondary hydroxy group of 2'-deoxy-3',5'-di-O-hexanoyl pyrimidine nucleosides was also reported[36] (Scheme 24).



Scheme 24

PFL can also catalyse the regioselective esterification of α-substituted cyclic acid anhydrides with ethanol in diisopropyl ether.[37] The lipase catalyses the reaction preferentially at the less hindered side (Scheme 25).

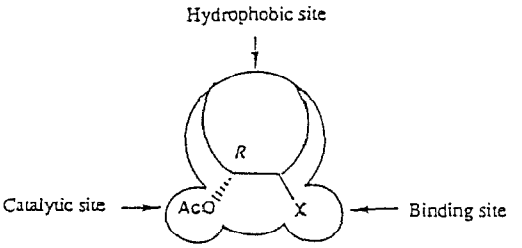


Scheme 25

6 . Model of PFL

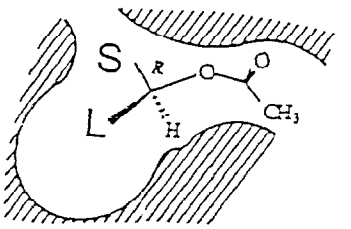
Unlike other enzymes, the selectivity of a lipase depends on the chemical structure of substrates and on their physical state. PFL can stereoselectively hydrolyse only 1-esters or 3-esters of triglyceride, a natural substrate. It appears that more hydrophobic esters are better substrates regardless of their physical state.[2]

A three site model[19] was proposed to explain the R-preference of hydrolysed alcohol by PFL which consists of i) a catalytic site to afford the alcohol with R-configuration, ii) a binding site for groups such as alkoxycarbonyl or acetate and iii) a hydrophobic site for the bicyclic ring system (Scheme 26).



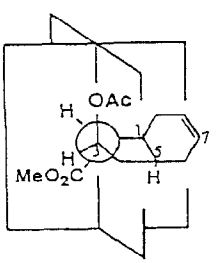
Scheme 26

Also an active site model can be schematized which contains catalyticlly active serine hydroxy site, a hydrophobic pocket and a niche that will accept only hydrogen directing the R-enantioselectivity (Scheme 27).

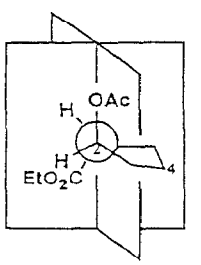


Scheme 27

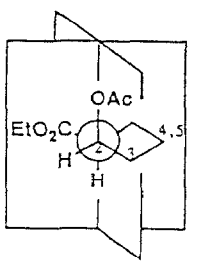
A stereomodel for PFL catalysed hydrolysis has also been proposed.[21] When the substrate is drawn in Newman projection with the acetate up, putting the C1-C2 bond perpendicular to an axis which is formed by two planes perpendicular to one another, active substrates bind to the active center in PFL only via the right hand volume as in (Scheme 28).



3β–Acetoxy-2α-methoxy-carbonyl-1αH, 5αH-bicyclo-[4.3.0]non-7-ene



Trans-1-Ethoxycarbonyl-2-acetoxycyclopentane



Cis-1-Ethoxycarbonyl-2-acetoxycyclohexane

Scheme 28

7 . Conclusion

This review demonstrates that PFL is an excellent chiral catalyst which can accept a variety of substrates. PFL has the ability to catalyse stereoselective reactions in water solution and can also tolerate organic solvents without loss of its catalytic activity. This chemo-enzymatic approach to asymmetric synthesis has been increasing. A working hypothesis for a model of PFL has appeared and is very useful and reliable to guide the correct selection of substrates with predicted stereochemistry. Understanding on the active site of PFL , however, is still at the infant stage and much work needs to be done in order to gain further insight .

8 . References

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