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Desymmetrisation of prochiral ketones using lipases

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Abstract

This review summarises recent advances in the use of lipase enzymes for the desymmetrisation of prochiral ketones. The method employed involves chemical conversion of the ketone to the racemic enol acetate followed by lipase-catalysed transesterification with *n*-butanol. A system for recycling the ketone in one-pot has been demonstrated and resulted in a high yield of a key enol ester intermediate for the synthesis of an important tachykinin NK-2 antagonist. 1,5-Disubstituted-8-oxabicyclo [3.2.1] octanones and 4,4-disubstituted cyclohexanones have been studied in detail and absolute configurations of two of the enzymatically derived enol esters determined.

Keywords: Desymmetrisation; Lipase; Enol ester; Prochiral ketone; NK-2 antagonist

1. Introduction

The desymmetrisation of prochiral ketones has become an important method for asymmetric synthesis. The asymmetric Baeyer Villiger reaction or deprotonation using chiral lithium amide bases serves to differentiate the two prochiral groups attached to the carbonyl of the ketone. Baeyer Villiger mono-oxygenase enzymes have shown promise for the desymmetrisation of prochiral and *meso* cyclohexanones [1], although the scale of these reactions is limited by the current availability of the enzymes and the expense of the requisite cofactors. Recently, cyclohexanone monoxygenase has been expressed in *Saccharomyces cerevisiae* [2] and *Escherichia coli* [3] and the enzyme appears to show identical activity and selectivity with the advantage that the downstream lactone metabolising enzymes are absent. There are limitations in the substrates that can be transformed, for example, 4-phenylcyclohexananoe is not a substrate for cyclohexanone mono-oxygenase [4]. Bolm has reported asymmetric Baeyer Villiger catalysts that use molecular oxygen based on chiral copper, [5] magnesium [6] and zirconium [7] complexes and Struckel [8] has developed a platinum catalyst using hydrogen peroxide as the terminal oxidant. Results with some of these catalysts are encouraging although e.e.'s are variable.

Chiral lithium amides have been employed by Koga and co-workers [9], Bunn and Simkins [10], and O'Brien [11][1] for the asymmetric deprotonation of 4-substituted cyclohexanones and prochiral aza- and oxa-bicyclic ketones. The chiral silyl enol ethers which result from enolate trapping can provide a handle for maintaining the newly introduced asymmetry by oxidative cleavage or electrophilic addition. High enantioselectivity has been achieved using a number of specialized chiral amines. However, the reactions are run at low temperatures (−78 or −100 °C) and

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[1] For review of chiral lithium amides in synthesis.

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require anhydrous conditions. Chiral lithium amide desymmetrisation of 8-oxabicyclic [3.2.1] ketones has shown significant promise giving intermediates for the synthesis of natural products such as lasonolide A [12] and the acetyl choline agonist (−)-anatoxin a [13].

This short review will summarise our recent results using a new lipase-based approach for the deracemisation of enol esters derived from two synthetically important classes of cyclic and bicyclic prochiral ketones. With the development of an efficient recycling system for the prochiral ketones, the reaction can be seen as a desymmetrisation of the ketone and provides a complementary method to the chiral lithium amide approach.

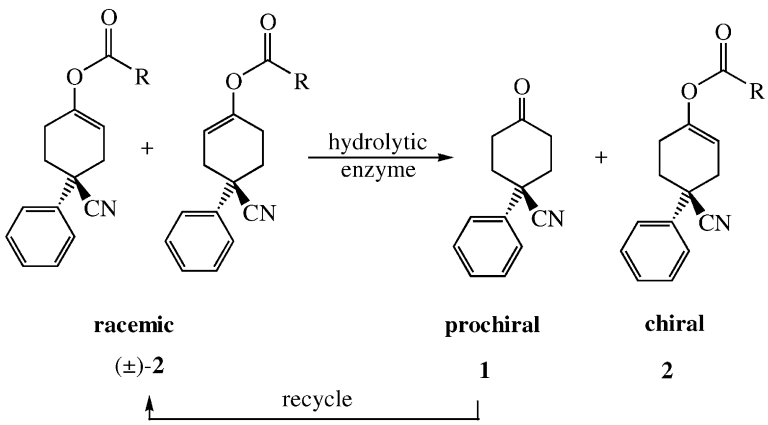
2. Development of a lipase-based approach for the desymmetrisation of prochiral ketones

Despite recent progress, methods to achieve the desymmetrisation of prochiral ketones which are amenable to scale-up using commercially available catalysts are required. We devised a new strategy that involves the enzymatic resolution of a racemic enol esters such as enol acetate **2** (R = Me) derived from the prochiral ketone **1** (Scheme 1). The attraction of such an approach is that the reaction product is the prochiral ketone and this can be chemically recycled. Hence, there is no loss of an unwanted enantiomer and the overall process can be viewed as a desymmetrisation of the prochiral ketone or deracemisation of the enol ester. Obviously, the success of such a process depends on the inherent selectivity of the enzyme step and the ability to recycle the ketone efficiently. Notably, the ketone **1** was not a substrate for cyclohexanone mono-oxygenase, or two Baeyer Villiger enzymes from *Pseudomonas putida* NCIMB 10007.

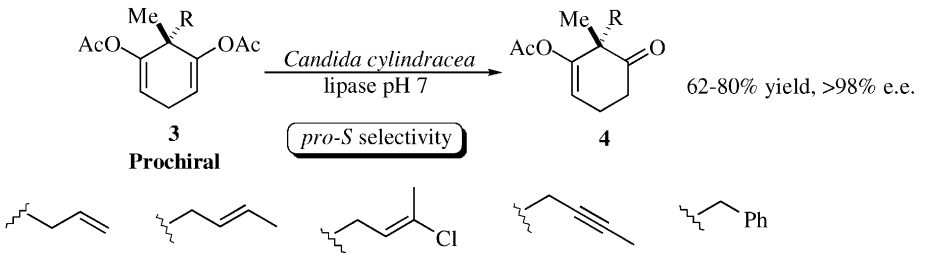
Ohta and co-workers [14] have reported the microbial hydrolysis of a range of enol esters derived from α-substituted cyclic and acyclic ketones. The biotransformations resulted in the asymmetric protonation of the enols giving chiral ketones. The facial selectivity of protonation for the incipient enol in our strategy was not of initial concern since we have no α-substituents in our enol ester substrates.

Duhammel et al. have reported the asymmetric hydrolysis of a series of prochiral 3,3-disubstituted 2,4-diacetoxycyclohexa-1,4-dienes **3** giving the unsymmetrical enol esters **4** in >98% e.e. following hydrolysis with *Candida cylindracea* lipase [15] Scheme 2.

In an attempt to find a suitable enzyme for the model substrate the enol acetate **2**, we screened a range of commercially available lipases and esterases in aqueous buffer. However, unfortunately very little enantioselectivity was found. The reaction was then carried out in organic solvent in order to facilitate a transesterification with *n*-butanol. The best enzyme for the model substrate was *Pseudomonas fluorescens* lipase (PFL), giving enantiomerically pure enol ester (*S*)-**2** after 67% conversion [16]. This equates to an *E*-value of 13, which is far from ideal for a resolution. However, the ketone could in principle be recycled. The



Scheme 1.



Scheme 2.

PFL reaction was carried out in a range of solvents (Table 1) and THF was found to be the optimal solvent with *E* values ranging from zero in phosphate buffer to 13 for THF. Reactions in toluene were generally faster than those in THF but selectivity was lower giving an *E* value of 6.5.

Variation of the acid component for the ester (R = Me, hexyl, dodecyl) did not affect the selectivity, although we did consider using the solubility difference between the dodecoyl ester and the ketone for separation prior to recycling the ketone.

The use of co-solvent systems has in some cases given significant improvements in selectivity for lipase-catalysed biotransformations. A range of organic solvents were tested using a 2:1 ratio of phosphate buffer:solvent for hydrolysis of the enol ester **2** (Table 2).

Most notable was the increase in rate in all cases when compared to the transesterification reaction in pure solvent. Interestingly, there is enantioselectivity, which does not occur in phosphate buffer alone. In fact, the results for the THF–buffer reaction are not dissimilar to those for the transesterification in THF,

Table 1
Variation in selectivity of PFL catalysed transesterification of substrate **2** with solvent

Solvent	Time (h)	Conversion (%)	e.e. (%)	*E*
THF	3.5	68	>99	13
EtOAc	2.5	41	48	9
Dioxane	4	72	94	7
Toluene	4	52	61	6.5
Et_2O	1	66	85	6
CH_3CN	6.5	52	53	5
Hexane	6.5	55	5.7	1
Buffer	2.5	56	0	0

Table 2
Effect of co-solvent mixtures on rate and enantioselectivity for hydrolysis of enol ester **2** with *Pseudomonas fluorescens* lipase

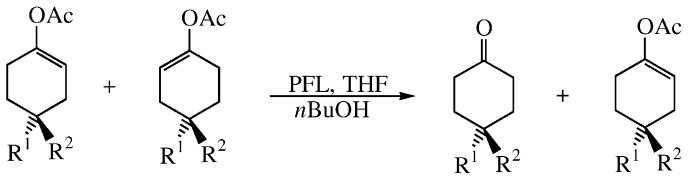
Co-solvent	Time (h)	Conversion (%)	e.e. (%)	*E*
THF	0.75	71	>99	11
CH_3CN	3.25	64	86	7
MeOH	1.5	78	89	4
EtOAc	2.25	59	56	4
Toluene	1.5	71	74	4
Et_2O	1.5	61	62	4
Dioxane	0.75	93	63	2

perhaps indicating the requirement of the solvent to maintain the enantioselective conformation of the enzyme. However, in most cases the enantioselectivity was lower and therefore the use of co-solvent appeared to provide no advantage other than a small increase in rate.

3. Resolution of 4,4-disubstituted cyclohex-2-enyl acetates

In order to test the scope of this biotransformation for the production of chiral enol esters derived from 4,4-disubstituted prochiral cyclohexanones, enol acetates **5**–**12** were synthesised and tested with PFL as new substrates (Scheme 3, Table 3) [17]. These were chosen with some synthetic targets in mind and to test the importance of the aromatic and cyano groups for selectivity. The enol acetate **5** was of particular interest since synthetic elaboration to a series of Pfizer NK-2 anatagonists was envisaged.

The 3,4-dichlorophenyl substrate **5** was resolved with slightly reduced but satisfactory selectivity giving the enol ester (*S*)-**5** in >99% e.e. after 70% conversion



Scheme 3.

Table 3
Biotransformation of substrates **2** and **5**–**12** with *Pseudomonas fluorescens* lipase

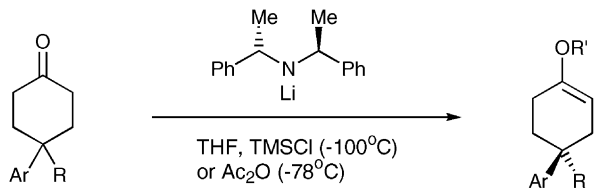
Substrate	R_1	R_2	Solvent	Conversion to ketone (%)	e.e. of enol acetate (%)	*E*
2	Ph	CN	THF	68	>99 (*S*)	13
5	3,4-Cl_2Ph	CN	THF	70	>99 (*S*)	11
5	3,4-Cl_2Ph	CN	Toluene	52	61	6.5
6	3,4-$(MeO)_2$Ph	CN	THF	71	95	7.4
7	2-Pyridyl	CN	THF	84	93	3.8
7	2-Pyridyl	CN	Toluene	71	94	7
8	Ph	CH_3	Hexane	75	17	1.3
9	Obn	CN	THF	73	91	5.6
10	Obn	C_2H	THF	82	12	1.2
11	Ph	CO_2CH_3	THF	62	7	1.2
12	CO_2CH_3	CN	THF	30	0	–

Reactions were carried out in organic solvent, 1eq. *n*BuOH, 30 mg of enol acetate (10 mg/ml) at room temperature. Enantiomeric excess is determined by chiral HPLC, Chiralcel OJ and Chiralpak AD.

to ketone. The reaction in toluene was less selective. Substrates **6** and **7** were both resolved with similar enantioselectivity in THF and toluene, respectively. Evidently, the active site of PFL can accommodate changes in the nature of the substitution on the phenyl ring of the substrate without affecting the selectivity significantly. The change in solvent requirement for optimum selectivity with substrate **7** may reflect small conformational changes in the enzyme in these solvents. Enol acetates derived from 4-methyl and 4-phenyl cyclohexanone did not undergo biotransformation in tetrahydrofuran but in hexane they were poorly resolved and reaction times were considerably longer [16]. This suggests a requirement for both an aromatic and a cyano group in the 4-position of the substrate for reasonable selectivity. Substrate **8** containing both 4-phenyl and 4-methyl groups was transformed in hexane with very low selectivity, supporting the finding with the earlier monosubstituted substrates that the cyano group is important for selectivity. Incubation of the benzyl-protected cyanohydrin enol acetate **9**, in which the aromatic group is more remote from the chiral center, gave comparable but slightly diminished selectivity when compared to substrates **2** and **5**–**7**. In substrate **10**, the 4-cyano was replaced by the linear 4-acetylene group which would place similar steric demands on the enzyme active site but would lack the polarity which might be required for binding. Indeed, the considerably lower selectivity with this substrate compared to substrate **9** confirmed this. Substrate **11**, in which the cyano was replaced with the polar ester group, and **12** in which the aromatic was replaced with the ester group both gave very poor or no selectivity, with substrate **12** reacting very slowly. These results confirmed the requirement for both an aromatic containing group and cyano group at the 4-position for reasonable enantioselectivity with this enzyme.

4. Desymmetrisation of 4,4-disubstituted cyclohexanones with chiral lithium amides

The use of chiral lithium amides for the desymmetrisation of prochiral ketones is well developed for a number of substrate types. A range of chiral



13 Ar = Ph, R = Me
1 R = Ph, R = CN

16 Ar = 3,4-Cl_2Ph, R = CN

14 Ar = Ph, R = Me, R' = $SiMe_3$, 81%, 71% e.e.
15 Ar = Ph, R = CN, R' = $SiMe_3$, 64%, 64% e.e.
2 R = Ph, R = CN, R' = Ac, 50%, 54% e.e.
5 Ar = 3,4-Cl_2Ph, R = CN, R' = Ac, 54%, 57% e.e.

Scheme 4.

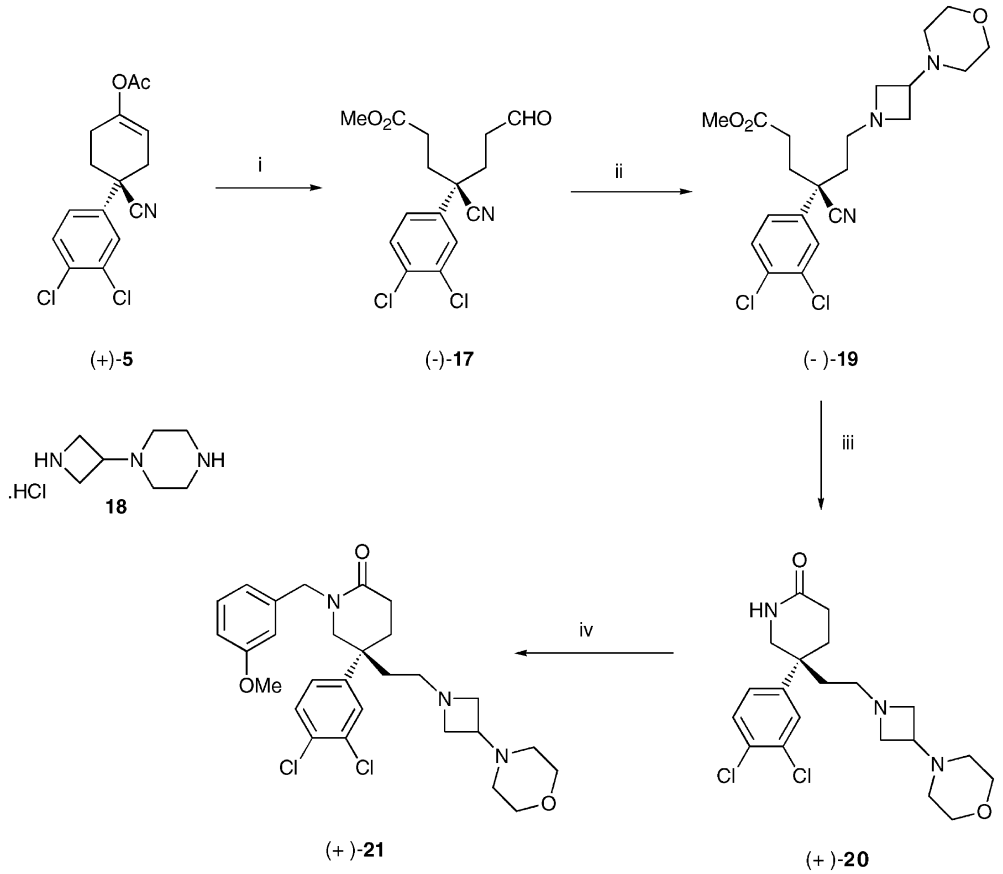
lithium amides have been developed which can, under appropriate conditions, give high enantiomeric selectivity for the formation of silyl enol ether products. As a comparison, a limited number of asymmetric deprotonation reactions with the prochiral ketone precursors to the current class of enol ester substrates were carried out. For these reactions the lithium amide derived from the commercially available (*S*)-(*R**,*R**)-(−)-bis(α-methylbenzyl)amine were used. Honda [18] reported the asymmetric deprotonation of 4-phenyl-4-methylcyclohexanone **13** at −100 °C to give the (*S*)-silyl enol ether **14** in 71% e.e. and 81% yield. Reaction of the 4-cyano-4-phenyl ketone **1** under the same conditions afforded a slightly lower 64% e.e. and 64% yield of the enol ether **15**. Asymmetric deprotonations on ketones **1** and **16** with this base at −78 °C with an external acetic anhydride quench gave the corresponding (*R*)-enol acetates **2** and **5** with 54 and 57% e.e., respectively (Scheme 4) [17].

Evidently, enantioselectivities for these 4,4-disubstituted cyclohexanones are moderate and not preparatively useful for chiral synthesis using the commercially available base. As enol esters can be regarded as enolate equivalents in the same way as silyl enol ethers, our enzymatic resolution method provides the best approach to obtaining these materials from this class of ketones.

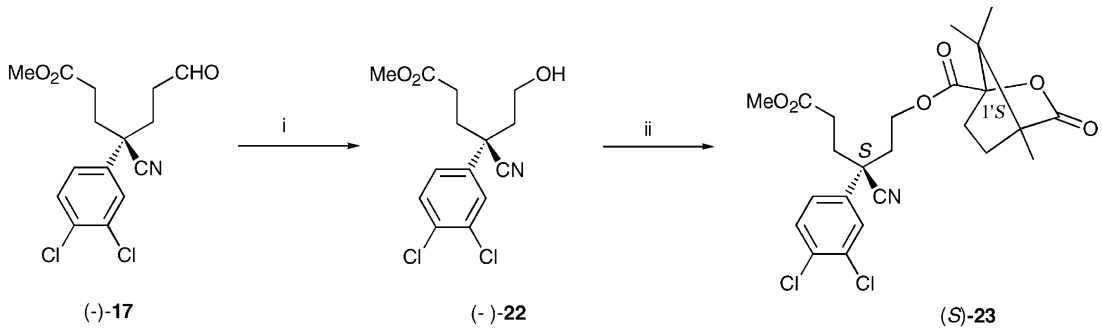
5. Application of enol ester (*S*)-3 in the synthesis of a tachykinin NK-2 antagonist

The sensoneuropeptide tachykinins, which include substance P and neurokinins A and B, are distributed in the peripheral and central nervous systems and are known to be involved in neurologic inflammation, pain transmission and bronchoconstriction [19]. The effects of these tachykinins are mediated through the activation of NK-1–3 receptors and new antagonists are being sought as a means of controlling pain and inflammation.

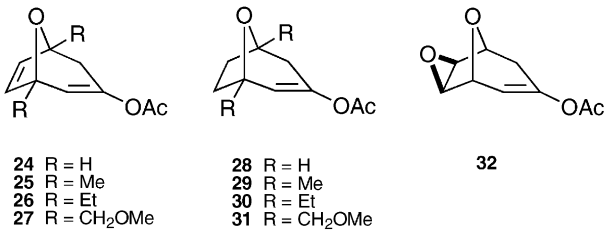
We have recently carried out the resolution of enol ester **5** (10 g) and shown application of enantiomerically pure (*S*)-**5** in the synthesis of an important class of tachykinin NK-2 antagonists (Scheme 5) [20]. The (*S*)-configuration for (+)-**5** was assumed by analogy to (*S*)-enol acetate **2** which had previously been determined by X-ray crystallographic analysis of a camphanic acid derivative [16]. Oxidative cleavage of the enol bond in (*S*)-**5** with ozone in methanol:dichloromethane (1:4) gave the aldehyde–ester (−)-**17** in 60% yield. Reductive amination with morpholinoazetidine hydrochloride **18** under hydrogenation conditions was not successful. The presence of the triethylamine used to release the free azetidine amine from its hydrochloride salt or the resultant triethylamine hydrochloride may have poisoned the palladium catalyst. However, prior formation of the imine between **18** and (−)-**17** in THF in the presence of triethylamine followed by reduction with sodium triacetoxyborohydride afforded the intermediate (−)-**19** in 91% overall yield. The reductive cyclisation of (−)-**19** to give lactam (+)-**20** was achieved in 86% yield using hydrogenation and Raney Nickel. Fortunately, no dechlorination of the phenyl ring was observed under these conditions. Lactam **20** underwent *N*-benzylation to furnish the target NK-2 antagonist (+)-**21** in 27% yield.



Scheme 5. Reagents and conditions: (i) O_3, MeOH/CH_2Cl_2(1:4), −78 °C then PPh_3, r.t. (60%); (ii) 'a' (**18**), THF, Et_3N, r.t., 'b' $NaB(OAc)_3H$, Et_3N (91%); (iii) H_2, Raney Ni, MeOH, 45 °C (86%); (iv) KH, 3-methoxy-benzylbromide, DMF,18-C-6, 0 °C (27%).



Scheme 6. Reagents and conditions: (i) $NaB(OAc)_3H$, AcOH, <20 °C (72%); (ii) (−)-1(*S*)-camphanic acid chloride, DMAP, pyridine, DCM (83%).



Scheme 7.

In order to confirm the suspected (*S*)-configuration of the 4-position of the enol acetate (+)-**5** the aldehyde (−)-**17** was converted into the crystalline camphanic ester derivative **23** *via* alcohol (−)-**22** shown in Scheme 6 [21]. Crystallisation of the ester **23** from benzene gave crystals suitable for X-ray analysis and the absolute configuration of the cyano substituted center was determined to be (*S*), thus confirming the configuration of the enol acetate (+)-**5** and the NK-2 antagonist (+)-**21** as (*S*).

6. Resolution of enol esters derived from prochiral 8-oxabicyclic [3.2.1] oct-6-en-3-ones

Screening of oxabicyclic enol acetate substrates **24**–**32** identified a lipase from *Humicola* sp. to be the best biocatalyst (where R = larger than H) for resolution by transesterification with *n*-butanol in hexane (Scheme 7, Table 4) [22]. Enol acetates **24** and **28** with no bridgehead substitution were not resolved by this enzyme. Introduction of bridgehead methyl groups in substrate **25** resulted in reasonable selectivity using the freeze-dried enzyme. However, use of the same enzyme which had been pre-adsorbed onto silica gel at pH 7, according to a recently described procedure, [23] resulted in a dramatic increase in reaction rate (110 min versus 82 h for ca. 50% conversion). Dry *n*-butanol was used instead of *n*-propanol to carry out the dehydration washing step after decanting the adsorbed enzyme since this was the alcohol used in the transesterification reaction. Hence, for accuracy the acronym BREP (butanol-rinsed enzyme preparation) was used.

Enantiomerically pure enol ester (*S*)-**25** ($[\alpha]_D = -53.5^\circ$) was isolated in 30% yield after chromatography. Biotransformation of related substrates **26** and **27** with the BREP gave a similar level of enantioselectivity ($E = 47$ and 48). However, the closely related saturated substrates **28**–**31** were transformed with much lower selectivity. From these results it is clear that the active site of the enzyme can tolerate quite wide

Table 4
Lipase resolution of enol acetates **24**–**32** with *Humicola* sp. lipase

Substrate enol acetate	Enzyme type	Reaction time	Conversion (%)	Isolated ketone (%)	Isolated yield of enol acetate (%)	e.e. (%) enol acetate	*E*
24	Freeze dried	24 h	51	–	–	0	–
25	Freeze dried	82 h	55	–	–	83	13
25	BREP[a]	110 min	49	36	37	84	45
25	BREP	1 h	67	36	30	>99	–
26	BREP	19 h	51	23	40	91	47
27	Freeze dried	5 days	0	–	–	–	–
27	BREP	48 h	53	46	32	96	48
28	Freeze dried	28 h	25	–	–	0	
29	BREP	31 h	51	–	–	42	3.5
30	BREP	30 h	0	–	–	–	–
31	BREP	28 h	35	37	53	12	–
32	BREP	3 h	70	31	23	95	7.8

[a] BREP = *n*BuOH rinsed enzyme preparation. Reactions were run using substrate (0.052 M), enzyme (60 mg/mM substrate) and *n*BuOH (2eq.) in dry hexane. Chiral analysis was done using a Chiralpack AD column eluting with hexane/*iso*-propanol.

variation at the bridgehead positions of the substrates but both reaction rate and selectivity are severely compromised upon saturation of the alkene in the 6,7-position of the ring system. Interestingly, intermediate but still useful selectivity ($E = 7.8$) was observed with the epoxide substrate **32** in which case it was necessary to run the reaction to 70% completion to leave highly enriched (95% e.e.) unreacted epoxy enol acetate **32**. The absolute configuration of the enantiomerically pure enol acetate (−)-**25** was determined as 1(*S*), 5(*S*) by X-ray crystallographic analysis of a camphanic ester derivative.

The 1,5-disubstituted chiral enol acetates described here can serve as chiral enolate equivalents and have not been previously available using chiral lithium amide methodology. In addition, the good enantioselectivity ($E > 45$) for three of the substrates makes recycling the prochiral ketone a viable approach to achieving a net desymmetrisation (see next section).

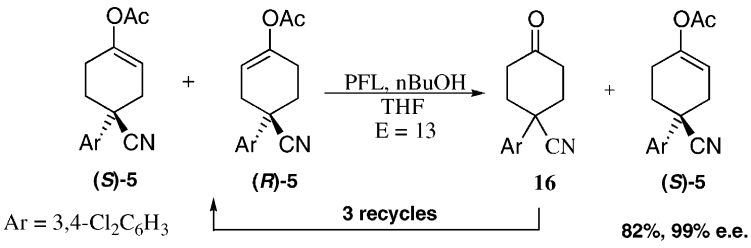
7. Recycling the ketone leading to desymmetrisation

In order to achieve a deracemisation of the enol ester **5** (or a desymmetrisation of the ketone **16**) in one pot, a system was devised whereby the enzyme was temporarily removed to allow for reformation of the enol ester using potassium *tert*-butoxide and isopropenyl acetate (Scheme 8). Fortuitously, the by-products of this recycle, acetone and *tert*-butanol, did not affect the activity or selectivity of the enzyme in subsequent cycles [24].

Using a kinetic analysis of cyclical reactions it was possible to calculate the degree of conversion required for each enzymatic step in order to regenerate enantiomerically enriched enol ester **5** with the optimum e.e. from the chemical recycle (Fig. 1).

For 100% theoretical yield, the $\text{e.e.}_{\max}$ of the process where the enzyme step has an E value of 13 can be calculated as 85.7% [$\text{e.e.}_{\max} = (E-1)(E+1)$]. Obviously, the e.e. can be higher if the yield is compromised. The lower line of the graph in Fig. 1 shows that the optimum e.e. which can be obtained after the first recycle is 37.3% and that this will correspond to having run the first lipase reaction to 56.5% conversion, the point at which $\text{e.e.}_{\max}$ is reached. The upper line shows the e.e.'s and the corresponding degrees of conversion that would theoretically be obtained for each cycle. The second enzyme reaction will start with an e.e. of 37.3% which equates with a theoretical 31.6% conversion and needs only to be run to the same end point ($\text{e.e.}_{\max}$) corresponding to (56.5–31.6 = 24.9% conversion).

In practise we obtained an 82% yield of enantiomerically pure enol ester (*S*)-**5** over four cycles by



Each Cycle

1. Run enzyme reaction to *ca* 90% e.e.
2. Remove enzyme
3. Add KO^{t}Bu and IPPA (1.5 eq. wrt residual ketone)
4. Add Dowex-H^+ 50X8-100
5. Remove resin and add enzyme and *n*BuOH

Scheme 8.

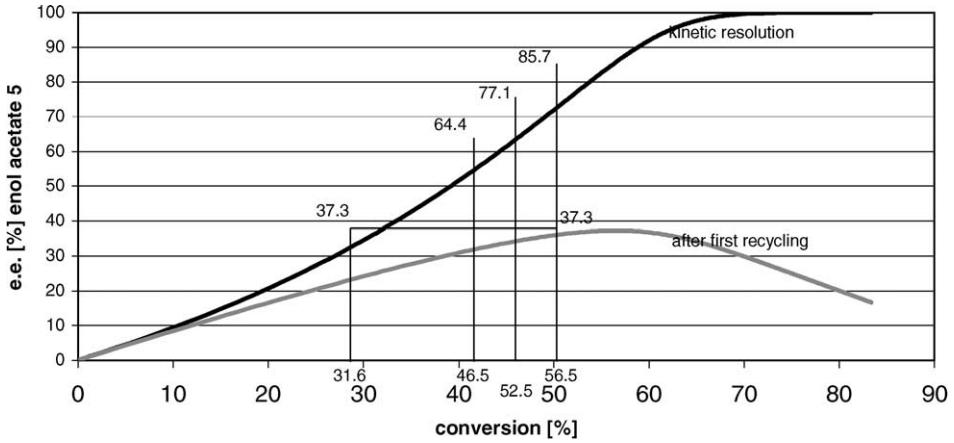


Fig. 1. Enantiomeric excess (e.e.) of enol acetate 5 after recycling of the ketone 16 vs. conversion for $E = 13$.

allowing the final enzyme reaction to run past the end point. This approach could be applied to any enol ester from any prochiral ketone. Given the number of lipases available, it is likely that one would find an enzyme with good enough selectivity for this approach for most substrate types. We are currently attempting to improve the selectivity of PFL by directed evolution in order to minimise the number of cycles necessary to obtain high yields using this process.

Acknowledgements

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References

[1] M.J. Taschner, D.J. Black, J. Am. Chem. Soc. 110 (1988) 6892;
M.J. Taschner, D.J. Black, Q.-Z. Chen, Tetrahedron Asymm. 4 (1993) 1387.
[2] J.S. Stewart, J.D. Stewart, K.W. Reed, C.A. Martinez, J. Zhu, G. Chen, M.M. Kayser, J. Am. Chem. Soc. 120 (1998) 354; J.S. Stewart, Curr. Opin. Biotechnol. 11 (2000) 363.
[3] S.D. Doig, L.M. O'Sullivan, S. Patel, J.M. Ward, J.M. Woodley, Enzyme Microb. Technol. 28 (2001) 265;
M.D. Mihovilovic, G. Chen, S. Wang, B. Kyte, F. Rochon, M.M. Kayser, J.D. Stewart, J. Org. Chem. 66 (2001) 733.
[4] C.T. Walsh, Y.-C. Jack Chen, Angew. Chem. Int. Ed. Engl. 27 (1988) 333.
[5] C. Bolm, T.K.K. Luong, G. Schlingloff, Synth. Lett. 10 (1997) 1151.
[6] C. Bolm, O. Beckmann, A. Cosp, C. Palazzi, Synth. Lett. 9 (2001) 1461.
[7] C. Bolm, O. Beckman, Chirality 12 (2000) 523.
[8] G. Struckel, Angew. Chem. Int. Ed. 37 (1998) 1199.
[9] T. Yamashita, D. Sato, T. Kiyoto, A. Kumar, K. Koga, Tetrahedron Lett. 37 (1996) 8195 (and references therein).
[10] B.J. Bunn, N.J. Simpkins, J. Org. Chem. 58 (1993) 533.
[11] P. O'Brien, J. Chem. Soc., Perkin Trans. 1 (1998) 1439.
[12] M. Nowakowski, H.M.R. Hoffmann, Tetrahedron Lett. 38 (1997) 1001.
[13] N.J. Newcombe, N.S. Simpkins, J. Chem. Soc., Chem. Commun. (1995) 831.
[14] K. Matsumoto, T. Oishi, T. Nakata, T. Shibata, K. Ohta, Biocatalysis 9 (1994) 97;
Y. Kume, H. Ohta, Tetrahedron Lett. 33 (1992) 6367;
K. Matsumoto, S. Tsutsumi, T. Ihori, H. Ohta, J. Am. Chem. Soc. 112 (1990) 9614.
[15] P. Renouf, J.-M. Poirier, P. Duhamel, J. Chem. Soc., Perkin. Trans. I 11 (1997) 1739;
P. Duhamel, P. Renouf, D. Cahard, A. Yebga, J.-M. Poirier, Tetrahedron Asymm. 4 (1993) 2447.
[16] A.J. Carnell, J. Barkely, A. Singh, Tetrahedron Lett. 38 (1997) 7781.
[17] G. Allan, A.J. Carnell, M.L. Escudero Hernandez, A. Pettman, J. Chem. Soc., Perkin. Trans. I (2000) 3382.
[18] T. Honda, N. Kimura, M. Tsubuki, Tetrahedron Asymm. 4 (1993) 21.
[19] C.A. Maggi, S. Manzini, Drugs Lung 507 (1994).;
D. Rees, Annu. Rep. Med. Chem. 28 (1993) 59;
J. Longmore, C.J. Swain, R.G. Hill, Drug News Perspect. 8 (1995) 5;
J. Fauchere, J. Pharmacol. Rev. 46 (1994) 551.
[20] G. Allan, A.J. Carnell, M.L. Escudero Hernandez, A. Pettman, Tetrahedron 57 (2001) 8193.

[21] A.J. Carnell, M.L. Escudero Hernandez, A. Pettman, J.F. Bickley, Tetrahedron Lett. 41 (2000) 6929.
[22] A.J. Carnell, S.A. Swain, J.F. Bickley, Tetrahedron Lett. 40 (1999) 8633.
[23] J. Partridge, P.J. Halling, B.D. Moore, J. Chem. Soc., Chem. Commun. 7 (1998) 841.
[24] G. Allan, A.J. Carnell, W. Kroutil, Tetrahedron Lett. 42 (2001) 5959.