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An Asymmetric, Chemo-Enzymatic Synthesis of *O*-Acetylcyanohydrins

Yuri N. Belokon,[a] A. John Blacker,[b] Lisa A. Clutterbuck,[c] David Hogg,[b] Michael North,*[c] and Christopher Reeve[d]

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A one-pot chemo-enzymatic synthesis of highly enantiomerically enriched *O*-acetylcyanohydrins has been developed. The bimetallic (salen)titanium complex **1** is used to convert aldehydes into nonracemic (*R*)-*O*-acetylcyanohydrins with 61 to 93% enantiomeric excess. A lipase enzyme is then used to hydrolyse the unwanted (*S*) enantiomer of the product, leaving (*R*)-*O*-acetylcyanohydrins with 80 to >99% enantiomeric excess and in 75 to 96% overall yield. Of ten lipase enzymes investigated, *Candida antarctica* lipase-B (CAL-B) has been shown to be the most suitable and the conditions for its use have been optimised. Although no single solvent has been found in which both catalyst **1** and CAL-B gave high reaction rates and enantioselectivities, two procedures to allow their sequential use without purification of the *O*-acetylcyanohydrin produced by catalyst **1** have been developed. In the first of these, the reaction with catalyst **1** is carried out in dichloromethane which is then removed and replaced with methyl *tert*-butyl ether prior to addition of the enzyme. In the second procedure, the first reaction is carried out in concentrated dichloromethane solution, and this is then just diluted with methyl *tert*-butyl ether prior to addition of the lipase.

Introduction

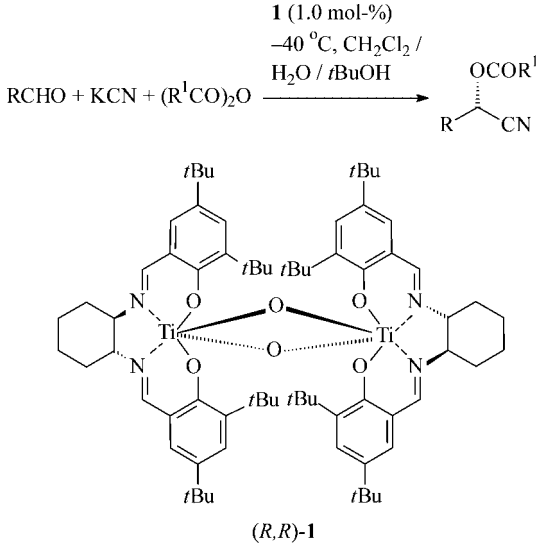
One of the main goals of green chemistry is the development of catalysts for organic synthesis which are mutually compatible and tolerant of any reagents and side products, thus allowing sequential transformations to be carried out in one pot without the need to isolate and purify reaction intermediates.[1] This is often achieved by preparing immobilised versions of catalysts which cannot interact with one another. However, the immobilisation methodology can adversely affect both the rate and enantioselectivity of a catalyst. In this manuscript, we demonstrate the use of an unmodified, solution-phase synthetic asymmetric catalyst and a lipase enzyme to achieve two sequential synthetic transformations, both of which occur enantioselectively.

[a] A. N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences,
117813, Moscow, Vavilov 28, Russian Federation
E-mail: yubel@ineos.ac.ru
[b] NPILPharma R+D,
P. O. Box 521, Leeds Rd., Huddersfield, West Yorkshire, HD2 1GA, United Kingdom
E-mail: john.blacker@npilpharma.co.uk
[c] School of Natural Sciences, Bedson building, University of Newcastle,
Newcastle upon Tyne, NE1 7RU, United Kingdom
E-mail: michael.north@ncl.ac.uk
[d] NPILPharma R+D,
P. O. Box 2, Belasis Avenue, Billingham, Cleveland, TS23 1YN, United Kingdom

Chiral cyanohydrins are versatile intermediates for the stereocontrolled synthesis of a wide range of 1,2-difunctional compounds such as α-hydroxy acids,[2] β-amino alcohols[3] and α-amino acids.[4] As a result, there is currently considerable interest in the development of new methods for the synthesis of nonracemic cyanohydrins.[5] Highly effective catalytic syntheses of cyanohydrins have been developed using both Lewis acid metal-based catalysts and enzymes. Metal-based catalysts are capable of inducing the asymmetric addition of a variety of cyanide sources (hydrogen cyanide,[6] trimethylsilyl cyanide,[7] potassium cyanide,[8] cyanoformates,[9] cyanophosphonates[10] etc.) to aldehydes and ketones with good to high enantioselectivity. Enzymatic approaches have been developed using either oxynitrilase enzymes[11] to catalyse the asymmetric addition of hydrogen cyanide to aldehydes, or using lipases to catalyse the asymmetric formation[12] or hydrolysis of cyanohydrin esters.[13]

We have developed bimetallic (salen)titanium complex **1** as a highly effective catalyst for asymmetric cyanohydrin synthesis.[14,15] Catalyst **1** is compatible with a variety of cyanide sources including trimethylsilyl cyanide,[16] cyanoformates,[17] acetyl cyanide[18] and potassium cyanide[19] to generate a variety of cyanohydrin derivatives derived from both aldehydes and ketones. An unique feature of complex **1** (along with the related (salen)V^V complex[17] and polymer-supported versions of these catalysts[8,20]) is its ability to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of an anhydride, giving cyanohydrin esters with up to 95% enantiomeric excess

(Scheme 1).[17] This chemistry has already been used in an asymmetric synthesis of α-acetoxy amides,[21] and for the synthesis of polymer-supported cyanohydrin esters.[22] However, whilst in the best cases excellent enantioselectivities are obtained, some substrates give products with *ee* <90%.[17] Because the products of this reaction are esters, it was attractive to investigate the combined use of catalyst **1** to synthesise chiral *O*-acetylcyanohydrins, and a suitable lipase enzyme to hydrolyse the minor enantiomer of the product back to the corresponding cyanohydrin, which would decompose back to the starting aldehyde under the reaction conditions. In this way, the enantiomeric excess of the *O*-acetylcyanohydrin would be enhanced without a major reduction in the chemical yield. Ideally, the two reactions should occur in a one-pot process without any need to isolate or purify the crude *O*-acetylcyanohydrin. In this manuscript, we describe the development of just such a one-pot, chemo-enzymatic synthesis of *O*-acetylcyanohydrins.



(*R*,*R*)-**1**

Scheme 1. Synthesis of cyanohydrin esters using catalyst **1**.

Results and Discussion

Initially, various lipase enzymes were screened for the hydrolysis of racemic *O*-acetylmandelonitrile [PhCH(OAc)-CN] **2**. Porcine pancreatic lipase, *Candida rugosa* lipase, *Pseudomonas fluorescens* lipase and *Pseudomonas cepacia* lipase, have all previously been used in the synthesis of optically active cyanohydrins,[23–27] but gave poor conversions and enantioselectivities with substrate **2**. *Rhizopus nevieus* lipase was also totally unreactive towards compound **2** under the reaction conditions studied. Selected results for other enzymes are given in Table 1.

Candida antarctica lipase-B (CAL-B) has previously been used to hydrolyse various *O*-acetylcyanohydrins, giving products with high enantiomeric excesses (up to >99%) in short reaction times, though at elevated temperature.[28] This temperature was incompatible with its use in situ with catalyst **1**, which requires ambient or lower temperatures to obtain high enantioselectivities. Fortunately, a reaction using this enzyme was found to proceed at room temperature giving a good conversion and enantioselectivity after one day (Table 1: Entry 1). By increasing the amount of enzyme, the reaction time could be reduced to 3 h and (*R*)-*O*-acetylmandelonitrile with 94% enantiomeric excess was obtained after just over 50% conversion (Table 1: Entries 2 and 3). The enantiomeric excess of the mandelonitrile produced in these reactions was not determined as this was not relevant to the ultimate aim of the project and was also expected to be unreliable due to spontaneous racemisation of mandelonitrile (vide infra). Changing the nucleophile from water to propan-2-ol or propan-1-ol so that the enzymatic reaction became a transesterification rather than a hydrolysis,[24] again had a beneficial effect, allowing the amount of enzyme to be reduced to 100 mg/mmol **2** whilst maintaining a rapid rate of reaction and a high enantioselectivity (Table 1: Entries 4 and 5). The solvent could be changed to methyl *tert*-butyl ether without adversely affecting the reaction rate or enantioselectivity (Table 1: Entries 6 and 7), but attempted use of dichloromethane (the optimal

Table 1. Lipase-catalysed resolution of racemic *O*-acetylmandelonitrile.

Entry	Lipase [mg/mmol **2**]	Solvent	Nucleophile	Time [h]	Conversion [%][a]	*ee* [%][b]
1	CAL-B (83)	toluene	water	19[c]	48	88 (*R*)
2	CAL-B (167)	toluene	water	18[c]	48	92 (*R*)
3	CAL-B (500)	toluene	water	3[c]	51	94 (*R*)
4	CAL-B (100)	toluene	*i*PrOH	6[c]	49	96 (*R*)
5	CAL-B (100)	toluene	*n*PrOH	4, 20[d]	15, 45[e]	21, 83[e] (*R*)
6	CAL-B (100)	MeO*t*Bu	*n*PrOH	4, 20[d]	45, 50[e]	82, >99[e] (*R*)
7	CAL-B (100)	MeO*t*Bu	*n*PrOH	18[c]	50	>99 (*R*)
8	CAL-B (100)	CH_2Cl_2	*i*PrOH	141[c]	48	84 (*R*)
9	ASL (100)	MeO*t*Bu	*n*PrOH	4, 20[d]	42, 63[e]	70, >99[e] (*R*)
10	ASL (100)	MeO*t*Bu	*n*PrOH	18[c]	53	>99 (*R*)
11	PSL (100)	MeO*t*Bu	*n*PrOH	4, 20[d]	46, 60[e]	85, >99[e] (*R*)
12	PSL (100)	MeO*t*Bu	*n*PrOH	18[c]	55	>99 (*R*)
13	PCL (100)	MeO*t*Bu	*n*PrOH	4, 20[d]	29, 47[e]	40, 88[e] (*R*)
14	CRE (100)	MeO*t*Bu	*n*PrOH	4, 20[d]	15, 36[e]	18, 56[e] (*S*)
15	CRE (100)	MeO*t*Bu	*n*PrOH	18[c]	34	51 (*S*)

[a] Determined by ^{1}H NMR spectroscopy with an error of +/– 4%. [b] Determined by chiral GC with an error of +/– 3%. [c] Reaction was stirred at 20 °C under nitrogen for the specified time. [d] Reaction was shaken at 20 °C under nitrogen and sampled after 4 h and 20 h. [e] first number refers to sample taken after 4 h and the second number to sample taken after 20 h.

solvent for catalyst **1**) resulted in a significantly lengthened reaction time (Table 1: Entry 8).

Alcaligenes sp. lipase (ASL), which has previously been used to enantioselectively acetylate 3-phenoxymandelonitrile,[29] was found to be highly reactive and enantioselective for transesterifications carried out in methyl *tert*-butyl ether (Table 1: Entries 9 and 10), but was both less reactive and less enantioselective when toluene or dichloromethane was used as solvent. Similar results were obtained with *Pseudomonas stutzeri* lipase (PSL) (Table 1: Entries 11 and 12), celite-immobilised *Pseudomonas cepacia* lipase (PCL) (Table 1: Entry 13) and *Candida rugosa* esterase (CRE) (Table 1: Entries 14 and 15), all of which gave the fastest and most enantioselective reactions in methyl *tert*-butyl ether. However, both the reactivity and enantioselectivity decrease in the order PSL > PCL > CRE. CRE was however notable as it hydrolysed the opposite enantiomer of the substrate to all of the other enzymes, leaving an excess of the (*S*) enantiomer of *O*-acetylmandelonitrile.

Enzymatic reactions are often carried out in shaken rather than stirred reaction vessels so as to avoid physical damage to the enzyme or its support. Therefore, some of the reactions described in Table 1 were carried out with magnetic stirring whilst others were agitated on a shaking plate. In many cases these reactions were directly comparable and demonstrated that the mode of agitation had no effect on the rate of reaction or enantioselectivity (compare the following pairs of Entries in Table 1: 6 and 7; 9 and 10; 11 and 12; 14 and 15). This was significant for the eventual aim of conducting the asymmetric cyanohydrin synthesis and enzymatic hydrolysis in a one-pot process.

Because of the above results, three enzymes: CAL-B, ASL and PSL were determined to be sufficiently active to justify further investigation of their reactivity. Whilst CAL-B[24] and ASL[25] have previously been shown to accept cyanohydrin substrates, PSL appears not have been previously investigated with this class of substrate. These three enzymes were therefore employed to enantioselectively hydrolyse a nonracemic sample of *O*-acetylmandelonitrile which had been prepared using catalyst **1** as previously reported.[17] Because all three enzymes selectively hydrolysed the (*S*) enantiomer of *O*-acetylmandelonitrile, a sample enriched in the (*R*) enantiomer was required and this was prepared with 77% enantiomeric excess using the (*S*,*S*) enantiomer of catalyst **1** and was purified by column chromatography prior to use in the enzymatic reaction. The enzymatic reactions were carried out using methyl *tert*-butyl ether as solvent and samples were withdrawn at regular intervals to allow both the progress of the reaction and the enantiomeric excess of the remaining (*R*)-*O*-acetylmandelonitrile to be determined. The results are shown in Table 2.

This study highlighted two significant factors. The first is that reactions catalysed by CAL-B are much faster than those catalysed by either of the other two enzymes (this may reflect the purity of the commercial enzyme preparation rather than any intrinsic rate difference) as CAL-B was able to increase the enantiomeric excess of (*R*)-*O*-acetylmandelonitrile to >99% in just 5 h (Table 2: Entry 4) whilst ASL and PSL both required reaction times of 23.5 h to achieve the same enantioselectivity (Table 2: Entries 11 and 18). CAL-B is also intrinsically more enantioselective, as it produces (*R*)-*O*-acetylmandelonitrile with >99% enantiomeric excess after hydrolysing just 10% of the substrate whilst ASL has to hydrolyse 31% of the *O*-acetylmandelonitrile to achieve the same enantiomeric excess and PSL has to hydrolyse 18% of the substrate. Both of these enzymes are clearly capable of hydrolysing both enantiomers of *O*-acetylmandelonitrile, whereas comparison of the data in Table 2 (Entry 4) with that in Table 1 (Entry 7) indicates that under these reaction conditions, CAL-B will not accept the (*R*) enantiomer of *O*-acetylmandelonitrile as a substrate. As a result, CAL-B was selected as the only enzyme to be used in further studies.

Table 2. Lipase-catalysed resolution of nonracemic *O*-acetylmandelonitrile.[a,b]

Entry	Lipase	Time [h]	Conversion [%][c]	*ee* [%][d]
1	CAL-B	1	3	83
2	CAL-B	2	5	88
3	CAL-B	3.5	8	95
4	CAL-B	5	11	>99
5	ASL	1	3	81
6	ASL	2	5	85
7	ASL	3.5	8	89
8	ASL	5	10	93
9	ASL	6	11	95
10	ASL	7.5	13	96
11	ASL	23.5	31	>99
12	PSL	1	3	82
13	PSL	2	4	84
14	PSL	3.5	6	87
15	PSL	5	7	90
16	PSL	6	8	91
17	PSL	7.5	9	93
18	PSL	23.5	18	>99

[a] Initial *ee* of *O*-acetylmandelonitrile = 77%. [b] All reactions were carried out at 20 °C in methyl *tert*-butyl ether using propan-1-ol as nucleophile and 100 mg of enzyme for every mmol of *O*-acetylmandelonitrile. [c] Conversions were determined by ^{1}H NMR spectroscopy. [d] *ee* Values were determined by chiral GC.

The nature and number of equivalents of alcohol used in the resolution of racemic *O*-acetylmandelonitrile was found not to have a major influence on the rate or enantioselectivity of the reaction. Thus, reactions carried out in methyl *tert*-butyl ether in the presence of 1–4 equiv. of propan-1-ol all gave 51–56% conversion after 22 h and the remaining (*R*)-*O*-acetylmandelonitrile had an enantiomeric excess of >99% in each case. However, use of a large excess of alcohol did have a small effect in retarding the enzymatic reaction as after 4 h reaction, the conversion decreased from 37% with 1 equiv. of propan-1-ol to 16% with 4 equiv. of propan-1-ol. Reactions were carried out using four different alcohols (propan-1-ol to hexan-1-ol), and almost identical conversions and enantioselectivities were obtained in each case. Therefore, use of 1 equiv. of propan-1ol was selected as the standard conditions for subsequent work.

The optimal concentration of *O*-acetylmandelonitrile was next determined by carrying out reactions at racemic mandelonitrile concentrations of 0.1–0.2 M, and analysing

both the conversion and enantioselectivity after 4 h reaction. A concentration of 0.15 M was found to be optimal (44% conversion and 77% *ee*), with both lower and higher substrate concentrations giving lower conversions (33% for 0.1 M and 19% for 0.2 M) and therefore lower apparent enantioselectivities (49% for 0.1 M and 23% for 0.2 M). The substrate to enzyme ratio was also optimised with reactions conducted using 50, 100, 125, 150, 175 and 200 mg of enzyme per mmol of substrate under the standard conditions developed above. Only at the two highest substrate to enzyme ratios had the reactions not reached completion (50% conversion) after 6 h, and all of the other reactions gave (*R*)-mandelonitrile with at least 95% enantiomeric excess. Therefore, use of 125 mg of enzyme per mmol of substrate was selected as the most effective amount of enzyme.

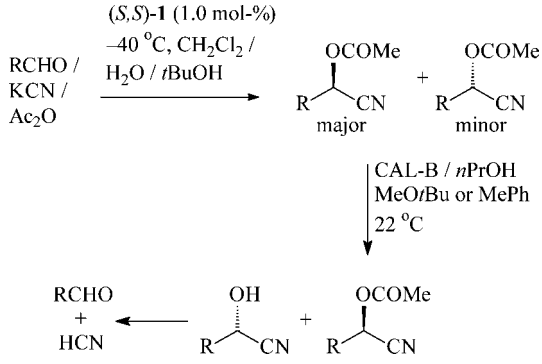
Under the optimised conditions of: substrate concentration 0.150 M, 125 mg of CAL-B/mmol substrate and 1 equiv. of propan-1-ol in methyl *tert*-butyl ether at room temperature, the resolution of a nonracemic (77% *ee*) sample of *O*-acetylmandelonitrile was again investigated. The enantiomeric excess of both the unreacted *O*-acetylmandelonitrile and the hydrolysed mandelonitrile were determined by chiral GC, and the results are shown in Table 3. As expected, the reaction proceeded rapidly under these conditions and after just 5 h all of the (*S*)-*O*-acetylmandelonitrile had been hydrolysed leaving (*R*)-*O*-acetylmandelonitrile with 99% enantiomeric excess. The enantiomeric excess of the hydrolysed mandelonitrile was found to decrease as the reaction progressed, presumably due to racemisation by a cyanide elimination–readdition mechanism.

Table 3. CAL-B-catalysed resolution of nonracemic *O*-acetylmandelonitrile.

Time [h]	*ee*, *O*-acetylmandelonitrile	*ee*, mandelonitrile	Conversion [%]
1	89 (*R*)	90 (*S*)	7
2	95 (*R*)	89 (*S*)	10
3.5	98 (*R*)	82 (*S*)	12
5	99 (*R*)	79 (*S*)	13

Having determined the optimal conditions for the enzymatic hydrolysis of *O*-acetylmandelonitrile, the most significant limitation in developing a chemo-enzymatic synthesis of *O*-acetylcyanohydrins appeared to be the differing solvent requirements of catalyst **1** and CAL-B. Catalyst **1** is most active in dichloromethane, whilst the enzyme only shows high reaction rates in methyl *tert*-butyl ether and toluene. Therefore, the use of other solvents for the asymmetric synthesis of *O*-acetylcyanohydrins using catalyst **1** under the conditions shown in Scheme 1 was investigated. However, reactions carried out in THF, diethyl ether, 1-butanol, 2-propanol, toluene or methyl *tert*-butyl ether were all much slower and less enantioselective than the corresponding reaction carried out in dichloromethane. Thus it appeared that it would not be possible to find a suitable single solvent for both the synthesis and hydrolysis of the cyanohydrins.

Nevertheless, the enzymatic results did indicate that a two step asymmetric synthesis of highly enantiomerically enriched cyanohydrins could be achieved as shown in Scheme 2. Thus, after the initial conversion of aldehydes into (*R*)-*O*-acetylcyanohydrins using the (*S*,*S*) enantiomer of catalyst **1** in dichloromethane, the solvent was removed in vacuo and without further purification, the *O*-acetylcyanohydrin was redissolved in methyl *tert*-butyl ether or toluene and treated with CAL-B to hydrolyse the small amount of the (*S*) enantiomer of the *O*-acetylcyanohydrin present. The highly enantiomerically enriched (*R*)-*O*-acetylcyanohydrin could then be isolated by column chromatography. The results obtained for a range of aldehydes are shown in Table 4.



Scheme 2. Chemo-enzymatic synthesis of (*R*)-*O*-acetylcyanohydrins.

As can be seen from Table 4, the presence of cyanide salts, titanium residues and unreacted acetic anhydride did not inhibit the hydrolytic activity of CAL-B in these reactions. Aromatic aldehydes which had been converted into (*R*)-*O*-acetylcyanohydrins with 70–90% *ee* by catalyst **1** were enantiomerically enriched to 90–99% *ee* after treatment with the lipase enzyme. In most cases, the enzymatic hydrolysis reaction was complete in 5–8 h, with only the sterically hindered *O*-acetylcyanohydrin derived from 2-methylbenzaldehyde requiring a longer reaction time. Two substrates (the *O*-acetylcyanohydrins of 3- and 4-methylbenzaldehyde) were subjected to enzymatic hydrolysis in toluene rather than methyl *tert*-butyl ether. Even with this nonoptimal solvent, these two substrates still gave (*R*)-*O*-acetylcyanohydrins with 97–98% *ee* values, though the reaction times were considerably lengthened compared to those typically needed for reactions carried out in methyl *tert*-butyl ether. This confirmed the general superiority of the ether solvent for the enzymatic hydrolyses.

Heteroaromatic aldehydes which were only moderate substrates for catalyst **1** were excellent substrates for CAL-B and the enantiomeric excess of the corresponding *O*-acetylcyanohydrins were raised from 61–77% to 88–98% after just 4–6.5 h treatment with the enzyme. Cinnamaldehyde was also an excellent substrate for the enzymatic hydrolysis and its (*R*)-*O*-acetylcyanohydrin could be isolated with 95% *ee* and in 80% yield. Aliphatic aldehydes are moderate substrates for catalyst **1**, and also gave mixed results in the subsequent enzymatic hydrolysis. Thus, whilst the *O*-acetylcyanohydrin of a primary aldehyde (nonanal) was an excellent substrate for CAL-B, *O*-acetylcyanohydrins of the second-

Table 4. A two-step, chemo-enzymatic synthesis of *O*-acetylcyanohydrins.

Aldehyde	*ee*, after (salen)Ti-catalysed synthesis[a]	*ee*, after enzymatic hydrolysis[b]	Time of enzymatic reaction [h]	Overall yield [%]
PhCHO	84	99	7	81
4-ClC_6H_4CHO	80	97	8	81
2-ClC_6H_4CHO	79	90	5	74
3-$MeOC_6H_4CHO$	87	94	5	84
2-MeC_6H_4CHO	72	90	27	69
3-MeC_6H_4CHO[c]	87	98	192	61
4-MeC_6H_4CHO[c]	81	97	168	50
2-Furaldehyde	77	98	6	78
Thiophene-2-carbaldehyde	61	88	6.5	72
Nicotinaldehyde	67	94	4	77
PhCH=CHCHO	75	95	5	80
$Me(CH_2)_7CHO$	77	92	7	66
Me_2CHCHO	47	74	23.5	46
CyCHO	60	68	21	65
Me_3CCHO	63	63	23	60

[a] Reaction conditions: aldehyde, potassium cyanide, acetic anhydride (mol ratio = 1:4:4), 1 mol% (*S*,*S*)-**1**, CH_2Cl_2, *t*BuOH, H_2O, –40 °C. [b] 125 Mg/mmol CAL-B, 1 equiv. isopropyl alcohol, 0.150 mol/L MeO*t*Bu. [c] Reaction carried out in toluene using isolated and purified *O*-acetylcyanohydrin.

Table 5. A one-pot, chemo-enzymatic synthesis of *O*-acetylcyanohydrins.

Aldehyde	*ee*, after (salen)Ti-catalysed synthesis[a]	*ee*, after enzymatic hydrolysis[b]	Time of enzymatic reaction [h]	Overall conversion [%]
PhCHO	76	97	26	84
4-ClC_6H_4CHO	89	>99	7	94
2-ClC_6H_4CHO	75	89	22	89
3-$MeOC_6H_4CHO$	93	97	23	96
2-MeC_6H_4CHO	64	80	22	90
PhCH=CHCHO	67	90	23.5	85
2-Furaldehyde	76	>99	23	86
Thiophene-2-carbaldehyde	70	95	8	83
Nicotinaldehyde	61	92	7.5	82
$Me(CH_2)_7CHO$	69	92	22	75

[a] Reaction conditions: aldehyde, potassium cyanide, acetic anhydride (mol ratio = 1:4:4), promoted by 1 mol% of (*S*,*S*)-**1**, CH_2Cl_2, *t*BuOH, H_2O, stirring at –40 °C. [b] 125 mg/mmol CAL-B, 1 equiv. isopropyl alcohol, 0.15 mol/L MeO*t*Bu added to the CH_2Cl_2 solution.

ary aldehydes 2-methylpropanal and cyclohexane carboxaldehyde were much more moderate substrates, requiring extended reaction times to show a moderate to marginal increase in enantiomeric excess. Finally, the *O*-acetylcyanohydrin of pivaldehyde was not a substrate for CAL-B, clearly indicating that this enzyme can only accommodate primary and secondary aldehydes within its active site.

Whilst the above process was effective in synthesising highly enantiomerically enriched cyanohydrins, the need to change the solvent between the two reactions was inconvenient, especially for large-scale reactions. Therefore, as a final stage of reaction optimisation, it was decided to investigate the compatibility of CAL-B to a mixed solvent system of dichloromethane and methyl *tert*-butyl ether. This would allow the asymmetric cyanation reaction to be carried out in pure dichloromethane followed by the addition of the enzyme and a fourfold excess of its preferred solvent to carry out the hydrolysis reaction. Results obtained for this process are shown in Table 5.

Under these conditions, CAL-B was found to retain its catalytic activity and ten different aldehydes were converted into the corresponding *O*-acetylcyanohydrins. In most cases, the final enantiomeric excess of the *O*-acetylcyanohydrin was comparable for reactions carried out with a change of solvent (Table 4) or under one-pot conditions (Table 5), though the latter reactions usually required longer reaction times for the enzymatic reactions. The only exception was the *O*-acetylcyanohydrin derived from 2-methylbenzaldehyde, which was obtained with 10% lower enantiomeric excess in the one-pot process. However, this difference is due to a change in the enantiomeric excess of the product at the end of the titanium-catalysed reaction, rather than any difference in the enzymatic reaction. In both cases, CAL-B raised the enantiomeric excess of the *O*-acetylcyanohydrin by 16–18% in 22–27 h.

Conclusions

We have demonstrated that a variety of lipases are capable of enantioselectively hydrolysing *O*-acetylcyanohydrins. From the lipases screened, CAL-B was selected as showing the most promising activity, and the conditions for its use with a range of *O*-acetylcyanohydrins have been optimised. No single solvent could be found in which both catalyst **1**

and CAL-B exhibited high activity, but two procedures to allow the combined use of the synthetic catalyst and enzyme were developed. These processes allowed a wide range of aromatic, heteroaromatic, and aliphatic aldehydes to be converted into the corresponding *O*-acetylcyanohydrins with higher enantiomeric excesses than could be obtained using catalyst **1** alone and higher yields than could be obtained using an enzyme to resolve the racemic *O*-acetylcyanohydrin. Although this chemistry has been demonstrated with CAL-B, it is clearly compatible with other lipase enzymes, so that in those cases where CAL-B does not give satisfactory results (e.g. secondary and tertiary aliphatic aldehydes), an alterative lipase enzyme could be used.

Experimental Section

Toluene was distilled from sodium prior to use. THF was dried by distillation from metallic sodium. CAL-B was obtained from Sigma, other enzymes were obtained from Europa Bioproducts Ltd. Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin layer chromatography was performed on polyester-backed sheets coated with silica gel 60 F254, both supplied by Merck. Chiral gas chromatography was performed on a γ-CD Butyryl, fused silica capillary column (30 m × 0.25 mm) using hydrogen as the carrier gas.

Optical rotations were recorded with a Perkin–Elmer 343 polarimeter in a thermostatted cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (g/100 mL). Infrared spectra were recorded with a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates. The characteristic absorption is reported as strong (s), medium (m) or weak (w) in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer. ^1H and ^{13}C NMR spectra were referenced to TMS and chemical shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s) or multiplet (m). Low- and high-resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea. The sample was ionised by electron ionisation (EI), chemical ionisation (CI) or electrospray ionisation (ESI). The major fragment ions are reported and only the molecular ions are assigned.

Caution: Many of the following experimental procedures involve the use of potassium cyanide, which is highly toxic and should only be handled in a well ventilated fume-cupboard and in compliance with all relevant safety protocols.

General Procedure for the Synthesis of Racemic *O*-Acetylcyanohydrins: Potassium cyanide (2.5 g, 39.2 mmol), *t*BuOH (1.0 mL, 10.3 mmol) and water (0.1 mL, 4.4 mmol) were stirred in CH_2Cl_2 (20 mL) at room temperature. The aldehyde (9.8 mmol) and acetic anhydride (4.0 g, 39.2 mmol) were added and the reaction monitored by GC until complete. The solid salts were then filtered and washed with CH_2Cl_2. The combined organic layers were evaporated in vacuo and the residual oil used for chiral GC calibration without further purification.

General Procedure for the Enzymatic Resolution of Racemic *O*-acetylmandelonitrile. Method A: This procedure was used for those reactions in Table 1 which were agitated by stirring. The appropriate nucleophile (11.4 mmol) was added to racemic *O*-acetylmandelonitrile (1.0 g, 5.7 mmol) in the specified solvent (57 mL) under N_2. The specified amount of a lipase enzyme was then added to the solution and the reaction mixture was stirred vigorously at room temperature. At suitable intervals (3–24 h depending on the nature and concentration of the enzyme), samples were taken from which the enzyme was removed by filtration and the solvent evaporated in vacuo. The residue was analysed by ^1H NMR spectroscopy and chiral GC in order to obtain the conversion and the enantiomeric excess of the (*R*)-*O*-acetylmandelonitrile. After the period of time specified in Table 1, the whole reaction was worked-up and analysed in the same way.

General Procedure for the Enzymatic Resolution of Racemic *O*-Acetylmandelonitrile. Method B: This procedure was used for those reactions in Table 1 which were agitated by shaking. To racemic *O*-acetylmandelonitrile (80 mg, 0.46 mmol) in a screw-cap vial was added the specified solvent (4.8 mL), and *n*PrOH (55 mg, 0.07 mL, 0.91 mmol). The lipase enzyme (46 mg) was then added to the solution and the reaction mixture was gently agitated on a spiro-mix at room temperature. After 4 h and 20 h, samples were taken from which the enzyme was removed by filtration and the solvent removed in vacuo. The residue was analysed by ^1H NMR spectroscopy and chiral GC in order to obtain the conversion and the enantiomeric excess of the (*R*)-*O*-acetylmandelonitrile.

General Procedure for the Enzymatic Resolution of Nonracemic *O*-Acetylmandelonitrile: This procedure was used for the reactions detailed in Table 2 and Table 3. *n*PrOH (450 mg, 0.58 mL, 7.52 mmol) was added to nonracemic (*R*)-*O*-acetylmandelonitrile[17] (659 mg, 3.76 mmol, *ee* 77%) in MeO*t*Bu (38 mL) under N_2. The lipase enzyme (376 mg) was added and the reaction was stirred vigorously at room temperature. At suitable intervals (1–6 h), samples were taken from which the enzyme was removed by filtration and the solvent removed in vacuo. The residue was monitored by ^1H NMR spectroscopy and chiral GC to obtain the conversion and the enantiomeric excess of the (*R*)-*O*-acetylmandelonitrile. After the period of time specified in Table 2 or Table 3, the whole reaction was worked-up and analysed in the same way.

General Procedure for the Chemo-Enzymatic Synthesis of Enantiomerically Enriched *O*-Acetylcyanohydrins. Method A: This method was used for the reactions detailed in Table 4. *t*BuOH (0.47 mL, 4.95 mmol), water (0.04 mL, 2.36 mmol) and the aldehyde (4.7 mmol) were added successively to a stirred solution of potassium cyanide (1.23 g, 18.8 mmol) and (*S*,*S*)-**1** (57 mg, 0.047 mmol) in CH_2Cl_2 (20 mL). The solution was then cooled to –80 °C, and acetic anhydride (1.8 mL, 18.8 mmol) was added. The yellow solution was then warmed to –40 °C and was stirred vigorously for 48 h. The reaction mixture was then concentrated in vacuo and the residue resuspended in MeO*t*Bu (35 mL). CAL-B (0.59 g) and *n*PrOH (0.35 mL) were added and the reaction stirred at room temperature for 7 h. At regular intervals, aliquots of the reaction mixture were removed, filtered, and analysed by chiral GC to determine when the enantiomeric excess of the *O*-acetylcyanohydrin stopped increasing. The reaction mixture was then passed through a pad of silica, eluting with MeO*t*Bu. The eluent was concentrated in vacuo and the residue was purified by column chromatography to give the pure *O*-acetylcyanohydrin as a pale yellow liquid.

General Procedure for the Chemo-Enzymatic Synthesis of Enantiomerically Enriched *O*-Acetylcyanohydrins. Method B: This method was used for the reactions detailed in Table 5. *t*BuOH (0.47 mL, 4.95 mmol), water (0.042 mL, 2.36 mmol) and the aldehyde (4.71 mmol) were added successively to a stirred solution of potassium cyanide (1.23 g, 18.8 mmol) and (*S*,*S*)-**1** (57 mg, 0.047 mmol) in CH_2Cl_2 (5 mL). The solution was then cooled to –80 °C and acetic anhydride (1.77 mL, 18.8 mmol) was added. The yellow solu-

tion was then warmed to –40 °C and was stirred vigorously for 48 h. The reaction mixture was then warmed to room temperature and MeO*t*Bu (35 mL), CAL-B (0.59 g) and *n*PrOH (0.35 mL) were added after which the reaction continued and was worked-up as for Method A.

(*R*)-*O*-Acetyl-2-hydroxy-2-phenylacetonitrile:[30] Solvent system for column chromatography: hexane/ethyl acetate, 7:1. Yield 0.66 g (81%). $[\alpha]_D^{20}$ = +8.8 (*c* = 1, $CHCl_3$) [ref.[28] $[\alpha]_D^{20}$ = +8.4 (*c* = 10, $CHCl_3$) for (*R*) enantiomer]. GC: initial temperature 120 °C, hold at initial temperature for 5 min then ramp rate 20 °C min^{-1}. Retention times: 8.0 min [(*R*) enantiomer] and 8.3 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-2-(4-chlorophenyl)acetonitrile:[31] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.60 g (81%). $[\alpha]_D^{20}$ = –14.1 (*c* = 1, $CHCl_3$) [ref.[29] $[\alpha]_D^{25}$ = –13.9 (*c* = 1, $CHCl_3$)]. GC: initial temperature 120 °C, hold at initial temperature for 5 min then ramp rate 20 °C min^{-1}. Retention times: 10.5 min (*R* enantiomer) and 10.8 min (*S* enantiomer).

(*R*)-*O*-Acetyl-2-hydroxy-2-(2-chlorophenyl)acetonitrile:[17] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.55 g (74%). $[\alpha]_D^{20}$ = +32.9 (*c* = 1, $CHCl_3$) [ref.[17] $[\alpha]_D^{25}$ = +27 (*c* = 1, $CHCl_3$) for (*R*) enantiomer with 88% *ee*]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 60.7, 115.5, 127.9, 129.8, 130.3, 130.6, 131.9, 133.9, 168.6 ppm. MS (EI): *m*/*z* (%) = 209 (8) [M^+], 167 (51), 43 (100). HRMS (CI): calcd. for $C_{10}H_{12}ClN_2O_2$ ($M + NH_4^+$): 227.0582; found 227.0580. GC: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 1 °C min^{-1}. Retention times: 50.9 min [(*R*) enantiomer] and 51.2 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-hydroxy-2-(3-methoxyphenyl)acetonitrile:[32] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.63 g (84%). $[\alpha]_D^{20}$ = +4.8 (*c* = 1, $CHCl_3$) [ref.[30] $[\alpha]_D^{20}$ –4.8 (*c* = 2, $CHCl_3$) for (*S*) enantiomer]. GC: initial temperature 120 °C, hold at initial temperature for 5 min then ramp rate 20 °C min^{-1}. Retention times: 10.9 min [(*R*) enantiomer] and 11.1 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-2-(2-methylphenyl)acetonitrile:[8] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.38 g (69%). $[\alpha]_D^{22}$ = +14.7 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, $ArCH_3$), 2.39 (s, 3 H, $COCH_3$), 6.50 (s, 1 H, CHCN), 7.2–7.6 (m, 4 H, ArCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 20.9, 61.4, 116.4, 127.2, 128.9, 130.3, 130.9, 131.7, 137.1, 169.3 ppm. IR (film): $\tilde{\nu}$ = 3028, 2250, 1755 cm^{-1}. MS (EI): *m*/*z* (%) = 189 (5) [M^+], 128 (100), 103 (37), 91 (26). HRMS (CI): calcd. for $C_{11}H_{15}N_2O_2$ ($M + NH_4^+$) 207.1128; found 207.1128. GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 17.5 min [(*R*) enantiomer] and 17.6 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-2-(3-methylphenyl)acetonitrile:[33] Purified by bulb to bulb distillation at 135 °C (1 Torr). Yield 0.33 g (61%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, $ArCH_3$), 2.31 (s, 3 H, $COCH_3$), 6.30 (s, 1 H, CHCN), 6.9–7.4 (m, 4 H, ArCH) ppm. GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 3 °C min^{-1}. Retention times: 23.86 min [(*R*) enantiomer] and 23.93 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-2-(4-methylphenyl)acetonitrile:[34] Purified by bulb to bulb distillation at 140 °C (1 Torr). Yield 0.27 g (50%). GC conditions: initial temperature 100 °C, ramp rate 2 °C min^{-1}. Retention times: 31.1 min (*R* enantiomer) and 31.5 min (*S* enantiomer).

(*S*)-*O*-Acetyl-2-hydroxy-2-(2-furanyl)acetonitrile:[30] Solvent system for column chromatography: hexane/ethyl acetate, 6:1. Yield 0.67 g (78%). $[\alpha]_D^{22}$ = –18.8 (*c* = 1, $CHCl_3$) [ref.[30] $[\alpha]_D^{20}$ = +24.3 (*c* = 1.6, $CHCl_3$) for the (*R*) enantiomer]. GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 11.4 min [(*R*) enantiomer] and 11.7 min [(*S*) enantiomer].

(*S*)-*O*-Acetyl-2-hydroxy-2-(2-thiophenyl)acetonitrile:[30] Solvent system for column chromatography: hexane/ethyl acetate, 7:1. Yield 0.68 g (72%). $[\alpha]_D^{22}$ –13.4 (c 0.71, $CHCl_3$) [ref.[30] $[\alpha]_D^{20}$ = +10.4 (*c* = 0.3, $CHCl_3$) for the (*R*) enantiomer]. GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 15.9 min [(*R*) enantiomer] and 16.1 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-2-(3-pyridinyl)acetonitrile:[35] Solvent system for column chromatography: hexane/ethyl acetate, 2:1. Yield 0.63 g (77%). $[\alpha]_D^{20}$ = +3.8 (*c* = 1, $CHCl_3$). MS (EI): *m*/*z* (%) = 176 (2) [M^+], 133 (20), 117 (15), 63 (21), 51 (21), 43 (100). HRMS (ES): calcd. for $C_9H_9N_2O_2$ [MH^+] 177.0569; found 177.0659. GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 18.0 min [(*R*) enantiomer] and 18.2 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-4-phenylbut-3-enenitrile:[36] Solvent system for column chromatography: hexane/ethyl acetate, 7:1. Yield 0.61 g (80%). $[\alpha]_D^{20}$ –32.8 (*c* = 1, $CHCl_3$) [ref.[34] $[\alpha]_D^{22}$ –22.7 (*c* = 0.7, $CHCl_3$) for (*R*) enantiomer with 69% *ee*.]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 61.9, 115.9, 118.7, 127.6, 129.3, 129.8, 134.8, 138.3, 169.3 ppm. GC conditions initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 0.5 °C min^{-1}. Retention times: 103.9 min [(*R*) enantiomer] and 106.5 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxydecanenitrile:[37] Solvent system for column chromatography: hexane/ethyl acetate, 7:1. Yield 0.49 g (66%). $[\alpha]_D^{22}$ = +64.8 (*c* = 1, $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.3, 22.6, 24.5, 28.7, 29.0, 29.2, 31.7, 32.2, 61.1, 116.9, 169.1. HRMS (CI): calcd. for $C_{12}H_{25}N_2O_2$ ($M + NH_4^+$) 229.1911; found 229.1906. GC conditions: initial temperature 120 °C, hold at initial temperature for 5 min then ramp rate 20 °C min^{-1}. Retention times: 9.2 min [(*R*) enantiomer] and 9.4 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-3-methylbutanenitrile:[38] Compound decomposed on attempted silica gel chromatography. Yield before chromatography 0.45 g (46%). $[\alpha]_D^{22}$ = +9.1 (*c* = 1, $CHCl_3$). GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 5.4 min [(*R*) enantiomer] and 5.6 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-cyclohexyl-2-hydroxyethanenitrile:[30] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.61 g (65%). $[\alpha]_D^{22}$ = +39.5 (*c* = 1.0, $CHCl_3$). GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 14.7 min [(*R*) enantiomer] and 14.9 min [(*S*) enantiomer].

(*R*)-*O*-Acetyl-2-hydroxy-3,3-dimethylbutanenitrile:[39] Solvent system for column chromatography: hexane/ethyl acetate, 4:1. Yield 0.52 g (60%). $[\alpha]_D^{22}$ = +65.9 (*c* = 1.0, $CHCl_3$) [ref.[40] $[\alpha]_D^{20}$ = +106 (*c* = 5, $CHCl_3$)]. MS (CI): *m*/*z* (%) = 156 (28) [MH^+], 140 (100), 129 (13). GC conditions: initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 5 °C min^{-1}. Retention times: 5.8 min [(*R*) enantiomer] and 5.9 min [(*S*) enantiomer].

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