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Synthetic and mechanistic studies on asymmetric cyanohydrin synthesis using a titanium(salen) bimetallic catalyst

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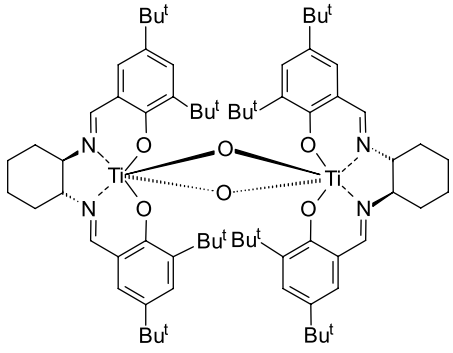
Abstract—A bimetallic titanium(salen) complex **1** was found to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes. Best results were obtained using 5 mol% of the catalyst at −40 °C and under these conditions, both aromatic and aliphatic aldehydes were converted into cyanohydrin carbonates with up to 99% enantiomeric excess. The same catalyst could also be used to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of propionic anhydride, leading to cyanohydrin esters. Mechanistic studies showed that the enantiomeric excess of the product increased during the early stages of this reaction. However, by adding a 'sacrificial aldehyde' this effect could be eliminated. The structure of the catalyst in solution was investigated using variable concentration, variable temperature and variable solvent NMR studies. These experiments showed that the catalyst exists as a mixture of monometallic **4** and bimetallic **1** species, a result which is consistent with previous mechanistic studies on the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones catalysed by the same catalyst. A mechanistic rationale for all of these observations is reported.

1. Introduction

Interest in asymmetric cyanohydrin synthesis has increased significantly in recent years due to the synthetic versatility of chiral cyanohydrins and their utility as chiral starting materials for natural product synthesis. Various types of catalyst are available for this reaction including oxynitrilase enzymes, cyclic-dipeptides, chiral Lewis-bases and chiral transition metal complexes.[1] However, most of these methods require the use of either hydrogen cyanide or trimethylsilyl cyanide as the cyanide source. Both of these reagents are volatile and hence hazardous, and trimethylsilyl cyanide is also expensive, especially for large scale use. Over the last eight years, we have developed titanium complex **1** as a highly active catalyst for the addition of trimethylsilyl cyanide to both aldehydes[2–4] and ketones.[5] This methodology has been applied to the asymmetric synthesis of fluorinated norepinephrines and fluorinated epinephrines.[6] A closely related vanadium(salen) complex was also found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes.[7] We have shown that complex **1** (and the related vanadium(salen) complex) will catalyse the asymmetric addition of potassium cyanide to an aldehyde in the presence of an anhydride, thus providing an asymmetric synthesis of cyanohydrin esters (Scheme 1).[8–11] This reaction has the advantage of avoiding the use of volatile cyanide reagents. In this manuscript, we give full details of our results using different anhydrides and report the results of mechanistic studies on this reaction.



Scheme 1.

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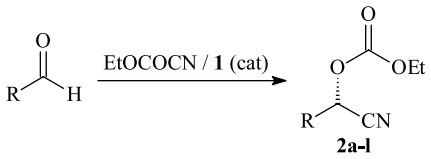
Cyanoformate esters (ROCOCN) are known to react with aldehydes and ketones, to form cyanohydrin carbonates.[12] Only recently, however, have asymmetric catalysts for this reaction been reported. In 2001, Tian and Deng showed that dimeric cinchona alkaloid derivatives would catalyse the asymmetric addition of ethyl cyanoformate to ketones, giving cyanohydrin ethyl carbonates with 59–97% enantiomeric excess.[13] It is notable that this first report involved the use of ketones rather than aldehydes as substrates. This reaction does however, require 10–30 mol% of the catalyst and reactions take up to 7 days. Subsequently, a heterobimetallic complex derived from three binol units, three lithium ions and a yttrium ion was shown by Shibasaki to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes, producing non-racemic cyanohydrin carbonates.[14] Best results were obtained at −78 °C using 10 mol% of the catalyst and three additives: water (30 mol%); butyl-lithium (10 mol%) and tri(2,6-dimethoxyphenyl)phosphine oxide (10 mol%). Under these conditions, products with 87–98% enantiomeric excess could be obtained. A third catalytic system was developed by Nájera et al. Thus, an aluminium binol complex was found to catalyse the asymmetric addition of methyl cyanoformate to aldehydes at room temperature.[15] Cyanohydrin carbonates with up to 80% enantiomeric excess were obtained from reactions employing 10 mol% of the catalyst along with 4 Å molecular sieves. The Nájera catalyst has also recently been reported to be compatible with the use of diethyl cyanophosphonate as the cyanide source.[16] Most recently, an oxynitrilase enzyme has been used to catalyse the asymmetric addition of ethyl cyanoformate to benzaldehyde, producing mandelonitrile ethyl carbonate with excellent (95–>99%) enantiomeric excess, but only moderate (maximum of 66%) chemical yield.[17]

In view of the above precedents, and the fact that cyanohydrin carbonates are configurationally stable and significantly less prone to hydrolysis than cyanohydrin trimethethylsilyl ethers, it was attractive to investigate the use of catalyst **1** in the asymmetric addition of ethyl cyanoformate to aldehydes (Scheme 2) and ketones. Ethyl cyanoformate is also less expensive than trimethylsilyl cyanide, and this, combined with the homogeneous nature of the reactions was expected have significant advantages for large scale preparations. It is also notable that the reaction shown in Scheme 2 is 100% atom-economical. In this manuscript we give full details of this work.[18]



2a-l

2a: R = Ph; **2b:** R = 4-$MeOC_6H_4$
2c: R = 3-$MeOC_6H_4$; **2d:** R = 2-$MeOC_6H_4$
2e: R = 4-MeC_6H_4; **2f:** R = 4-$F_3CC_6H_4$
2g: R = 4-ClC_6H_4; **2h:** R = PhCH=CH
2i: R = C_8H_{17}; **2j:** R = Me_2CH
2k: R = Cy; **2l:** R = Me_3C

Scheme 2.

We have previously reported the results of extensive studies to investigate the mechanism by which complex **1** catalyses the asymmetric addition of trimethylsilyl cyanide to aldehydes.[4] In this manuscript, we present additional evidence on the structure of complex **1** in solution which supports this mechanism and we show how the mechanism can be extended to reactions involving potassium cyanide or ethyl cyanoformate.

2. Results and discussion

2.1. Asymmetric synthesis of cyanohydrin ethyl carbonates

Initial studies were carried out using benzaldehyde as the substrate. The addition of ethyl cyanoformate (2 equiv) catalysed by complex **1** was studied under various conditions as shown in Table 1. First reactions were carried out in dichloromethane at a low temperature to enhance any enantioselectivity and with 1 mol% of the catalyst as this amount had previously been found to be optimal for reactions involving potassium cyanide.[8] When the reaction was carried out at −85 °C, no product was detected (Table 1: entry 1). Raising the reaction temperature to −73 °C did give (*S*)-mandelonitrile ethyl carbonate **2a** with a highly encouraging 94% enantiomeric excess though the reaction required 48 h to go to completion (Table 1: entry 2). The absolute configuration of product **2a** was determined by comparison of its specific rotation with literature data.[14a] At temperatures above −73 °C, the reaction rate increased, but at the expense of a reduction in the enantiomeric excess of the product. Thus, at −40 °C (Table 1: entry 3) the reaction was complete in 19 h, but the product was obtained with only 83% enantiomeric excess. Attempts to reduce the amount of catalyst to 0.1 mol% (the optimal amount for the addition of trimethylsilyl cyanide to aldehydes[2]) gave unsatisfactory results even at room temperature (Table 1: entries 4 and 5).

Whilst the result at −73 °C (Table 1: entry 2) was encouraging, the long reaction time was felt to be impractical. Therefore, the effect of increasing the amount of catalyst was investigated to see if similar enantiomeric excess could be obtained at a temperature where the rate of reaction was faster. Gratifyingly, the use of 5 mol% of catalyst **1** at −40 °C resulted in the complete formation of (*S*)-**2a** with 95% enantiomeric excess after a reaction time of 18 h (Table 1: entry 6). This combination of catalyst mol%, reaction temperature, and product enantiomeric excess is a significant improvement on any of the previously known catalysts[13–15] and was taken to be the optimal conditions for the use of complex **1** since a further increase in the amount of catalyst used (Table 1: entry 7) was not beneficial.

The effect of the reaction solvent was investigated using 5 mol% of catalyst **1**, a reaction temperature of −40 °C, and 1.2 equiv of ethyl cyanoformate. The results are shown in Table 2. These reactions were significantly slower than the optimised conditions, an effect which is mainly due to the reduced concentration of ethyl cyanoformate used (compare Table 1: entry 6 with Table 2: entry 7). An aromatic solvent gave product **2a** with a very low enantiomeric excess (Table

Table 1. The asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1**[a]

Entry	Temperature (°C)	**1** (mol%)	Time (h)	Completion (%)	ee[b] (%)
1	−85	1	19	<3	
2	−73	1	48	100	94 (*S*)
3	−40	1	19	100	83 (*S*)
4	−40	0.1	72	<3	
5	25	0.1	148	<3	
6	−40	5	18	100	95 (*S*)
7	−40	10	51	100	93 (*S*)

[a] All reactions were carried out using 2 equiv of ethyl cyanoformate in dichloromethane.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

2: entry 1). Oxygenated solvents gave a greater degree of asymmetric induction, though the reactions failed to go to completion after 2 days and ethyl acetate gave a particularly slow reaction (Table 2: entries 2–4). Only chloroform gave a high conversion to product with a high enantiomeric excess (Table 2: entry 5), though even in this case the enantiomeric excess of product **2a** was 7% lower than that obtained when dichloromethane was used as the solvent (Table 2: entry 7). Use of the non-polar chlorinated solvent, tetrachloromethane, resulted in a very slow reaction even though the reaction was carried out at −20 °C. Insufficient product was formed after 4 days to allow the enantiomeric excess to be determined (Table 2: entry 6). On the basis of these results, it was apparent that dichloromethane was both the most effective and the most convenient solvent for these reactions.

The addition of ethyl cyanoformate to other aldehydes was then investigated under the optimized conditions (Table 1: entry 6). The results are shown in Table 3. Electron rich aromatic aldehydes (all three isomers of methoxybenzaldehyde and 4-methylbenzaldehyde) were found to be excellent substrates for this reaction, giving cyanohydrin carbonates **2b–e** in high chemical yield and with excellent enantiomeric excesses (94–99%) (Table 3: entries 2–5). Cinnamaldehyde was also found to be an excellent substrate giving cyanohydrin carbonate **2h** with 94% enantiomeric excess (Table 3: entry 8). The electron deficient aromatic aldehyde 4-trifluoromethylbenzaldehyde was a very fast reacting substrate (Table 3: entry 6), though it gave product **2f** with a relatively low enantiomeric excess (76%). This may be due to a competing uncatalysed addition of ethyl cyanoformate to this particularly reactive aldehyde. 4-Chlorobenzaldehyde was however an excellent substrate, giving cyanohydrin ethyl carbonate **2g** in high yield and with 94% enantiomeric excess (Table 3: entry 7). For all of these reactions, the use of 2 equiv of ethyl cyanoformate was necessary for the reactions to be complete in less than 20 h. The quantity of ethyl cyanoformate used could however be reduced to just 1.2 equiv, at the expense of extended reaction times of 45–68 h.

A series of aliphatic aldehydes was also studied as substrates for this reaction (Table 3: entries 9–12) and all gave products (**2i–l**) with similar enantiomeric excesses (76–84%). The primary aldehyde nonanal gave the product with the highest enantiomeric excess (Table 3: entry 9), but there was no significant difference between the enantioselectivity observed with the secondary and tertiary aldehydes (Table 3: entries 10–12). For aliphatic aldehydes, the amount of ethyl cyanoformate used could be reduced to 1.2 equiv without the reaction time being extended beyond 20 h. The only exception to this was pivaldehyde which is a slow reacting substrate, presumably for steric reasons (Table 3: entry 12).

Two ketones, acetophenone and 2-butanone, were also investigated as substrates. Catalyst **1** is known to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones,[5] but no conditions were found under which it would catalyse the addition of ethyl cyanoformate to either of these ketones. Even at room temperature and with prolonged reaction times, only unreacted starting materials were observed.

2.2. Asymmetric synthesis of cyanohydrin esters

The reaction shown in Scheme 1 provides a very convenient, one-pot synthesis of configurationally stable cyanohydrin esters. This reaction was developed using

Table 2. The influence of the solvent on the asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1**[a]

Entry	Solvent	Time (h)	Conversion (%)	ee[b] (%)
1	Toluene	45	100	30
2	EtOAc	90	23	42
3	Ether	47	73	51
4	Thf	73	49	52
5	Chloroform	53	96	84
6	Tetrachloromethane[c]	96	<5	
7	Dichloromethane	42	98	91

[a] All reactions were carried out using 1.2 equiv of ethyl cyanoformate.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.
[c] Reaction carried out at −20 °C.

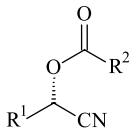
Table 3. The asymmetric addition of ethyl cyanoformate to aldehydes catalysed by complex **1** in dichloromethane

Entry	Aldehyde (product)	Time (h)	EtOCOCN (equiv)	Yield (%)[a]	ee[b] (%)
1	PhCHO (**2a**)	18	2	90	95
2	4-$MeOC_6H_4CHO$ (**2b**)	18	2	92	95
3	3-$MeOC_6H_4CHO$ (**2c**)	17	2	94	99
4	2-$MeOC_6H_4CHO$ (**2d**)	48	1.2	95	98
5	4-MeC_6H_4CHO (**2e**)	48	1.2	67 (95)	94
6	4-$(F_3C)C_6H_4CHO$ (**2f**)	6	2	84	76
7	4-ClC_6H_4CHO (**2g**)	68	1.2	96	94
8	PhCH=CHCHO (**2h**)	45	1.2	47 (99)	94
9	$C_8H_{17}CHO$ (**2i**)	22	2	54	88
10	Me_2CHCHO (**2j**)	20	1.2	23 (88)	79
11	CyCHO (**2k**)	18	1.2	82	79
12	Me_3CCHO (**2l**)	48	1.2	69	73

[a] After purification by distillation. Number in brackets is the yield before distillation.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

acetic anhydride, and was found to give good to excellent enantioselectivities with a range of aromatic and aliphatic aldehydes.[8,9,11] Whilst acetic anhydride is the experimentally most convenient anhydride for synthetic work, we decided to see if the structure of the anhydride had any influence on the enantioselectivity, rate, or yield of the reaction.[10] Three anhydrides were chosen for an initial study, propionic anhydride, pivalic anhydride and benzoic anhydride. Propionic anhydride is only slightly larger than acetic anhydride, whilst pivalic anhydride is significantly sterically hindered. Thus, comparison of these two anhydrides with acetic anhydride would allow the influence of steric effects to be investigated. In contrast, benzoic anhydride was included as it has very different electronic properties to the three aliphatic anhydrides.[19] Both racemic[20–22] and non-racemic[23–25] cyanohydrin esters derived from all three of these anhydrides have previously been reported.

An initial study was carried out under the reaction conditions shown in Scheme 1, using benzaldehyde as the substrate and the three different anhydrides. The reactions were monitored by GC and the enantiomeric excess of the product **3b–d** was determined by chiral GC. The results of this study are shown in Table 4. Compared to previous work with acetic anhydride (Table 4: entry 1), the use of propionic anhydride (Table 4: entry 2) or pivalic anhydride (Table 4: entry 3) was found to have little effect on the enantioselectivity of the reaction. However, benzoic anhydride gave a product **3d** with significantly lower enantiomeric excess (Table 4: entry 4). Reactions involving propionic, pivalic or benzoic anhydride were much slower than reactions using acetic anhydride, requiring at least 48 h to go to completion. The use of benzoic anhydride resulted in a particularly slow reaction.



3a: R^1 = Ph; R^2 = Me
3b: R^1 = Ph; R^2 = Et
3c: R^1 = Ph; R^2 = CMe_3
3d: R^1 = Ph; R^2 = Ph
3e: R^1 = PhCH=CH; R^2 = Et
3f: R^1 = PhCH=CH; R^2 = CMe_3
3g: R^1 = 4-$(F_3C)C_6H_4$; R^2 = Et
3h: R^1 = 4-$(F_3C)C_6H_4$; R^2 = CMe_3
3i: R^1 = 3-$MeOC_6H_4$; R^2 = Me
3j: R^1 = 3-$MeOC_6H_4$; R^2 = Et
3k: R^1 = 4-$MeOC_6H_4$; R^2 = Me
3l: R^1 = 4-$MeOC_6H_4$; R^2 = Et
3m: R^1 = Me_2CH; R^2 = Me
3n: R^1 = Me_2CH; R^2 = Et
3o: R^1 = Me_3C; R^2 = Me
3p: R^1 = Me_3C; R^2 = Et
3q: R^1 = 2-MeC_6H_4; R^2 = Et
3r: R^1 = 3-MeC_6H_4; R^2 = Et
3s: R^1 = 4-MeC_6H_4; R^2 = Et
3t: R^1 = 4-ClC_6H_4; R^2 = Et
3u: R^1 = C_8H_{19}; R^2 = Et
3v: R^1 = Cy; R^2 = Et

Based on the above results, the use of benzoic anhydride was discontinued. However, both propionic and pivalic anhydride were felt to be worthy of further investigation since although they offered no improvement in enantioselectivity in the case of benzaldehyde, this would not necessarily be the case for other aldehydes. Therefore, a range of aromatic, aliphatic, and α,β-unsaturated aldehydes were studied with these two anhydrides, and the results are shown in Table 5. Two additional aldehydes

Table 4. The asymmetric addition of potassium cyanide to benzaldehyde catalysed by complex **1** in the presence of different anhydrides

Entry	Anhydride	Time (h)	Product	Conversion (%)	ee[a] (%)
1	Acetic	10	**3a**	93	90[8]
2	Propionic	48	**3b**	100	92
3	Pivalic	48	**3c**	85	88
4	Benzoic	72	**3d**	95	56

[a] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

Table 5. The asymmetric addition of potassium cyanide to aldehydes catalysed by complex **1** in the presence of different anhydrides[a]

Entry	Aldehyde	Anhydride	Product	Time (h)	Conversion (%)	ee[b] (%)
1	PhCH=CHCHO	Propionic	**3e**	48	73 (62% isolated yield)	95
2	PhCH=CHCHO	Pivalic	**3f**	72	50	75
3	4-$(CF_3)C_6H_4CHO$	Propionic	**3g**	50	100	94
4	4-$(CF_3)C_6H_4CHO$	Pivalic	**3h**	50	100	62
5	3-$MeOC_6H_4CHO$	Acetic	**3i**	10	99	93[8]
6	3-$MeOC_6H_4CHO$	Propionic	**3j**	48	100	90
7	4-$MeOC_6H_4CHO$	Acetic	**3k**	10	74	93[8]
8	4-$MeOC_6H_4CHO$	Propionic	**3l**	48	100 (71% isolated yield)	91
9	Me_2CHCHO	Acetic	**3m**	10	62	72[8]
10	Me_2CHCHO	Propionic	**3n**	62	100	17
11	Me_3CCHO	Acetic	**3o**	10	40	62[8]
12	Me_3CCHO	Propionic	**3p**	48	100	78
13	2-MeC_6H_4CHO	Propionic	**3q**	28	100	81
14	3-MeC_6H_4CHO	Propionic	**3r**	36	98	95
15	4-MeC_6H_4CHO	Propionic	**3s**	36	98	89
16	4-ClC_6H_4CHO	Propionic	**3t**	16	100	90
17	$C_8H_{17}CHO$	Propionic	**3u**	50	74	82
18	CyCHO	Propionic	**3v**	72	95	41

[a] All reactions were carried out at −40 °C in dichloromethane in the presence of water (0.5 equiv) and *tert*-butanol (1.0 equiv).
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

(cinnamaldehyde and *para*-trifluoromethylbenzaldehyde) were investigated with both propionic and pivalic anhydrides (Table 5: entries 1–4). However, the products obtained using pivaldehyde (**3f** and **3h**) had enantiomeric excesses at least 20% lower than those obtained using propionic anhydride (**3e** and **3g**), so the use of pivalic anhydride was not pursued further. Whilst most of the cyanohydrin esters were found to be chemically and configurationally stable, the products obtained from *para*-trifluoromethylbenzaldehyde (**3g** and **3h**) were both found to racemize on standing at room temperature. Thus, over a period of 3 days, the enantiomeric excess of compound **3g** decreased from 94 to 78% and that of **3h** decreased from 62 to 48%.

To allow a further direct comparison between the use of acetic and propionic anhydrides, four aldehydes previously used as substrates with acetic anhydride were investigated using propionic anhydride as well. The first two aldehydes chosen were the electron rich aromatic aldehydes 3- and 4-methoxybenzaldehyde. For both of these substrates, the products derived from acetic (**3i** and **3k**) and propionic (**3j** and **3l**) anhydrides were obtained with essentially identical enantiomeric excesses (Table 5: entries 5–8). The other two aldehydes used in this study were aliphatic, and in this case a significant difference between the two anhydrides was observed. In the case of 2-methyl-propanal, product **3m** obtained using acetic anhydride was found to have a much higher enantiomeric excess (72%) than product **3n** (17%) derived from propionic anhydride (Table 5: entries 9 and 10). By contrast, for cyanohydrin esters **3o** and **3p** derived from pivaldehyde, product **3p** obtained from propionic anhydride had a higher enantiomeric excess (78%) than product **3o** (62%) derived from acetic anhydride (Table 5: entries 11 and 12). Thus, whilst for aromatic aldehydes there is little or no difference in the enantioselectivity observed with acetic and propionic anhydrides, for aliphatic aldehydes the structure of the anhydride does appear to play a major role in determining the enantioselectivity of the process. Finally, four aromatic and two aliphatic aldehydes not previously used as substrates with acetic anhydride were investigated as substrates with propionic anhydride (Table 5: entries 13–18). Of the aromatic substrates, only the *ortho*-substituted aldehyde gave a product **3q** with an enantiomeric excess significantly below 90% (Table 5: entry 13). For *meta*- and *para*-substitued benzaldehydes, products with enantiomeric excesses >89% were consistently obtained irrespective of the electronic nature of the substituent (Table 5: entries 3, 6, 8, 14–16). The primary aldehyde nonal (Table 5: entry 17) gave product **3u** with a higher enantiomeric excess than that observed for secondary or tertiary aliphatic aldehydes (compare entry 17 with entries 10, 12, and 18). Cyclohexane carboxaldehyde gave product **3v** with a rather low enantiomeric excess (Table 5: entry 18), though not as low as that observed for product **3n** derived from 2-methyl propanal.

2.3. Variation of enantiomeric excess with time

Reactions carried out at −40 °C using propionic anhydride were sufficiently slow that they could be easily monitored by chiral GC. This revealed that the enantiomeric excess of the product (mandelonitrile propionate **3b**) increased significantly during the course of the reaction as shown in Figure 1. Thus, after 1 h of reaction, the enantiomeric excess

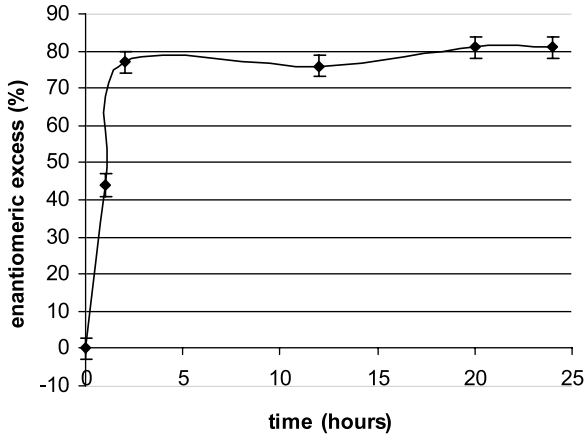


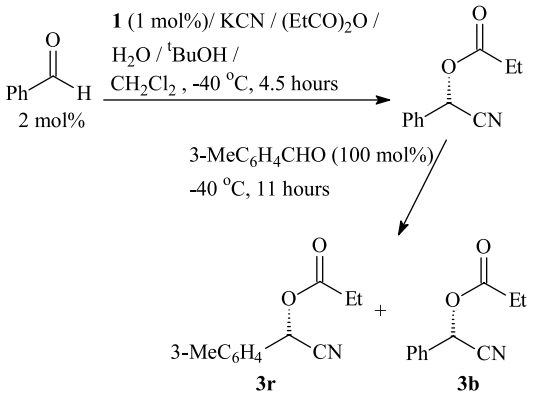
Figure 1. The variation of the enantiomeric excess of product **3b** with time. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC.

of the product was just 44%. After 24 h however, the enantiomeric excess of compound **3b** had increased to 81%.

The most likely explanation for this effect is that complex **1** is only slowly converted into species on the catalytic cycle, and during the early stages of the reaction, less enantioselective catalysis occurs due to other species. Details of the mechanisms of these reactions will be discussed in Section 2.5. However, this suggested a way of potentially increasing the enantiomeric excess of products **3**. Addition of a small amount of one aldehyde (a 'sacrificial aldehyde') should convert complex **1** into a species on the catalytic cycle. A few hours later, the real aldehyde could be added. In this way, the enantiomeric excess of the second aldehyde should not be reduced by competing processes with low or no enantioselectivity in the early stages of the reaction.

To test this hypothesis, a reaction was carried out as shown in Scheme 3. In this reaction, benzaldehyde functions as the 'sacrificial aldehyde' and 3-methylbenzaldehyde as the real substrate. Initially, catalyst **1** (1 mol% relative to the amount of 3-methylbenzaldehyde to be added later) and benzaldehyde (2 mol%) were added under standard conditions and allowed to react for 4.5 h. At this stage, 3-methylbenzaldehyde (100 mol%) was added and the reaction allowed to continue. The enantiomeric excess of both products (**3b** and **3r**) was simultaneously monitored by chiral GC, and the results are shown in Figure 2.

The experiment was at least partially successful, since it is quite clear that the enantiomeric excess of product **3r** remains constant at 90% throughout the reaction. At the end of the reaction, both aldehydes had undergone greater than 90% conversion to cyanohydrin propionates. However, the enantiomeric excess of product **3r** obtained in this way was actually slightly lower than the 95% obtained using only 3-methylbenzaldehyde as substrate (Table 5: entry 14). One explanation for this is that the catalytically active species formed in the reaction depend on the aldehyde from which they are formed. For example, a molecule of cyanohydrin could be bound to a titanium ion during the catalytic cycle. The catalyst obtained in this sacrificial experiment would then be different to that obtained in a normal reaction and so could exhibit different enantioselectivity. To further investigate this effect, the experiment was reversed: 3-methylbenzaldehyde (2 mol%) was used as the sacrificial aldehyde and benzaldehyde as the actual substrate. As Figure 3



Scheme 3.

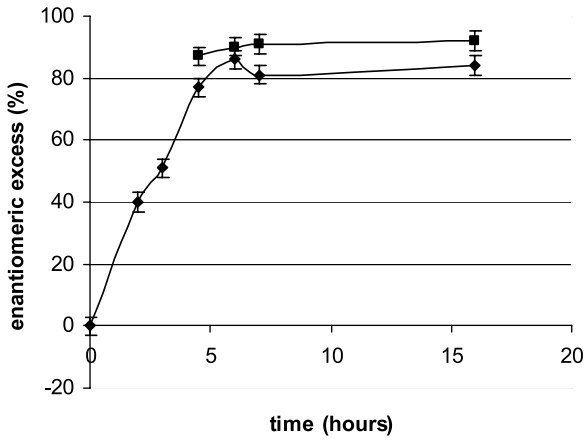


Figure 2. The variation of the enantiomeric excess of products **3b** and **3r** with time when benzaldehyde is used as a 'sacrificial' aldehyde. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC. Diamonds refer to product **3b**, and squares to product **3r**.

shows, exactly the same effects were observed: the enantiomeric excess of the sacrificial aldehyde increased during the reaction, but that of the real substrate stayed constant. However, the enantiomeric excess of product **3b** obtained in this way (80%) was again lower than that obtained using benzaldehyde as the only substrate (92%, Table 4: entry 2).

To try to find a sacrificial aldehyde system which did give enhanced enantioselectivities, four different sacrificial aldehydes with differing electronic properties were studied. In each case, benzaldehyde (90 mol%) was used as the real substrate and 10 mol% of the sacrificial aldehyde was used. The reactions were not followed by chiral GC, but Table 6 records the enantiomeric excess of product **3b** isolated in each case. The results of this series of experiments (Table 6: entries 1–4) were remarkably consistent; product **3b** was obtained with 78–80% enantiomeric excess whatever the nature of the sacrificial aldehyde. Finally, we carried out an experiment in which benzaldehyde was used as both the sacrifical aldehyde (10 mol%) and the real substrate

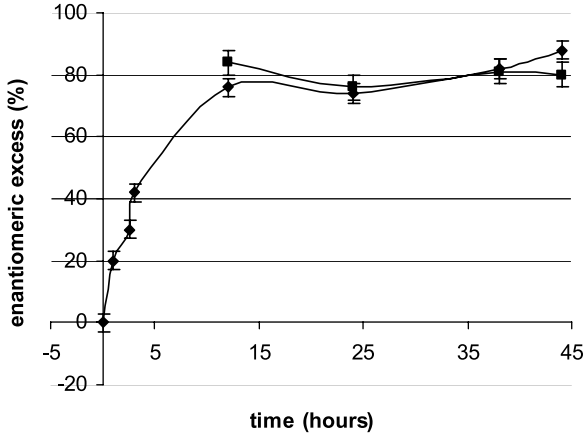


Figure 3. The variation of the enantiomeric excess of products **3b** and **3r** with time when 3-methylbenzaldehyde is used as a 'sacrificial' aldehyde. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC. Diamonds refer to product **3r**, and squares to product **3b**.

Table 6. The use of different sacrificial aldehydes for the asymmetric synthesis of product **3b**

Entry	Sacrificial aldehyde	ee[a] of **3b** (%)
1a	Nonal	80
2	Cinnamaldehyde	80
3	4-Methoxybenzaldehyde	80
4	4-Trifluoromethylbenzaldehyde	78
5	Benzaldehyde	80

[a] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

(90 mol%). This was expected to give product **3b** with 92% enantiomeric excess (cf. Table 4: entry 2), but actually again gave product **3b** with just 80% enantiomeric excess (Table 6: entry 5).

To explain these results, we propose that the sacrificial aldehyde does achieve its role of converting precatalyst **1** into species which lie on the catalytic cycle, but that these species are unstable in the absence of a high concentration of aldehyde. Thus, by the time that the real substrate is added (typically 4–5 h), some of the catalyst has decomposed, resulting in a reduced mol% of the catalyst being available to carry out the catalysis, and hence a lower enantiomeric excess of the final product.

2.4. Structure of the catalyst and its significance

During the course of this work, we studied the nature of catalyst **1** in solution. It has previously been determined by X-ray crystallography that the catalyst exists as a bimetallic complex in the solid state.[3] Kinetic studies on the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones catalysed by complex **1** however, indicated that the catalyst dissociated in solution to form both monometallic and bimetallic species.[4]

Routine ^{1}H NMR spectra (recorded in $CDCl_3$) obtained during the preparation of batches of catalyst **1** exhibited significant variability which initially led to concerns about the purity of the catalyst and its true structure. However, a variable concentration NMR study showed that the ^{1}H NMR spectrum of the catalyst was highly concentration dependent, with the changes in the aromatic and imine hydrogen region (6–9 ppm) being particularly pronounced. A representative set of spectra recorded in deuterated chloroform are shown in Figure 4.

At the highest concentration studied (0.0822 M), four aromatic peaks and two imine signals are observed as expected for bimetallic structure **1**. Only very small peaks corresponding to any other species are visible in the spectrum (Fig. 4a). However, as the concentration of the NMR solution is decreased, the intensity of the minor peaks increases (Fig. 4b and c), until at a concentration of 5×10^{-4} M, all the signals are of comparable intensity (Fig. 4d). At still lower concentrations, the signals corresponding to the originally minor species become dominant (Fig. 4e), until at the lowest concentration we could acquire a spectrum (8.3×10^{-6} M), the original signals virtually disappear from the spectrum (Fig. 4f).

Both species present in the spectra shown in Figure 4 give rise to two imine signals and four aromatic signals. Thus, in both cases the salen ligand lacks C_2 symmetry. These results indicate that catalyst **1** exists in chloroform solution as an equilibrium mixture of dimeric **1** and monomeric **4** species as shown in Scheme 4. At high concentrations, formation of the dimeric species is favoured, whilst at lower concentrations, formation of the monomeric species becomes more favourable. Dimeric species **1** has overall C_2 symmetry, but within each salen ligand the two aromatic rings are diastereotopic due to the *cis*-β conformation forced upon the ligand by the two bridging oxygens.[3] The monomeric complex **4** is square pyramidal and so again lacks C_2-symmetry. Asymmetric cyanation reactions carried out using catalyst **1** are typically carried out at a catalyst concentration between 8×10^{-4} and 1×10^{-2} M depending on the cyanide source. (With trimethylsilyl cyanide only 0.1 mol% of catalyst is needed;[3] the potassium cyanide/acetic anhydride system requires 1 mol% catalyst;[8] and for use of ethyl cyanoformate as the cyanide source, 5 mol% of catalyst is necessary[18]). These concentrations are all covered by the spectra shown in Figure 4a–d in which a significant amount of both monomeric and dimeric species are present. The equilibrium constant between the dimeric **1** and monomeric **4** species (calculated using data from the spectrum obtained at 0.02 M) was determined to be 3×10^{-3} M.

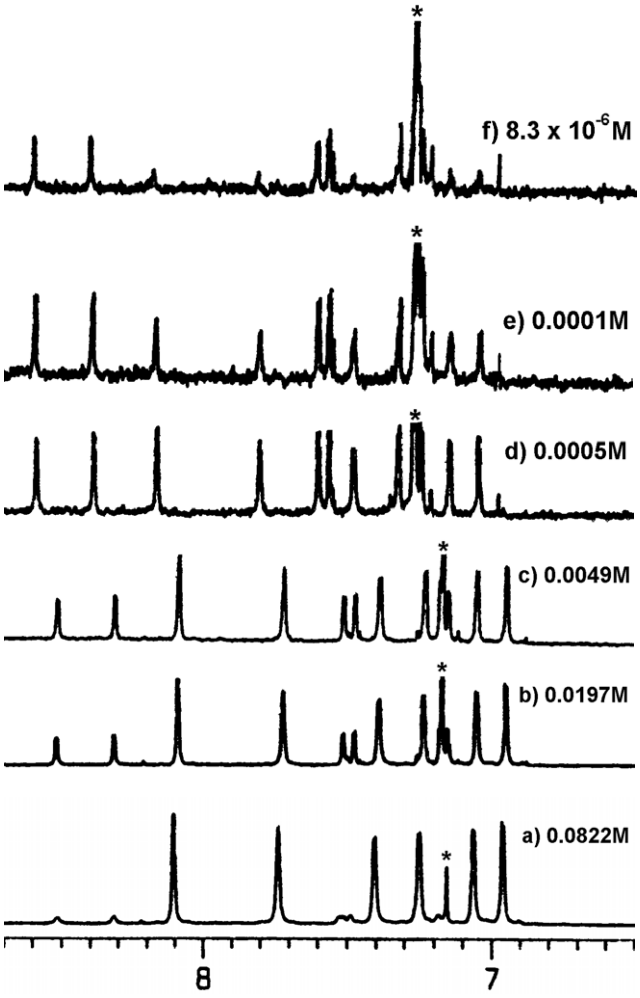
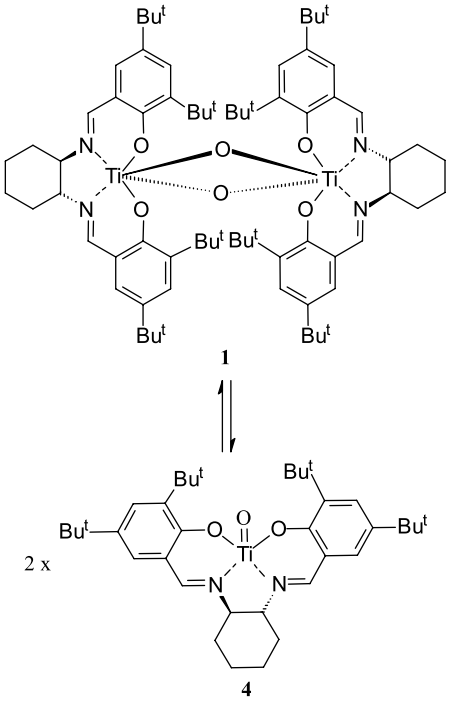


Figure 4. ^{1}H NMR spectra of compound **1** in $CDCl_3$ at different concentrations. *Signal due to $CHCl_3$.

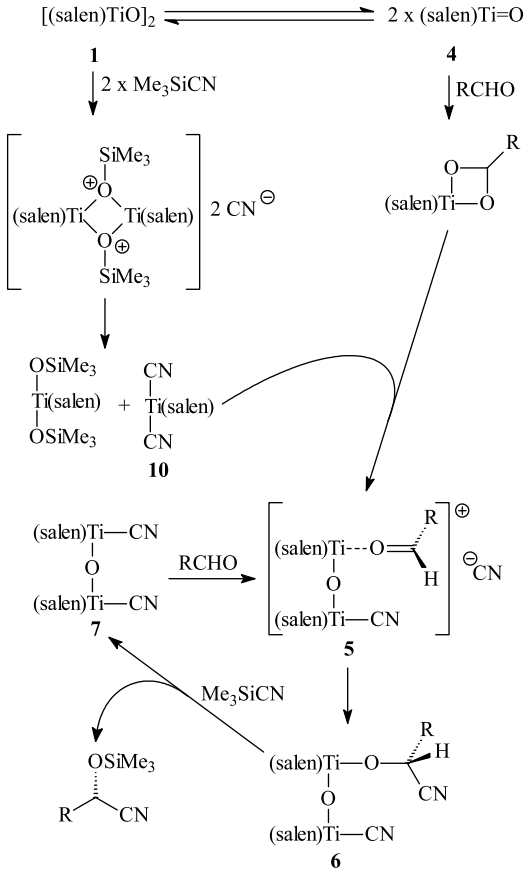


Scheme 4.

A variable temperature study of catalyst **1** in $CDCl_3$ at 0.01 M concentration was also undertaken. Between 213 and 333 K, no significant changes in chemical shift were observed. However, as the temperature was lowered, the signals for the minor species **4** became significantly sharper and decreased in intensity. Thus, at 333 K the ratio of the minor to major signals is 0.25:1 and this decreases to 0.1:1 at 213 K. This is consistent with the equilibrium shown in Scheme 4, since at higher temperatures, more energy is available to break the relatively weak Ti–O bonds, and hence the amount of monomeric species **4** present will increase. The X-ray structure of compound **1** shows that the central Ti_2O_2 unit is rectangular, with two normal Ti–O bonds and two longer bonds.[3] Cleavage of the latter is all that would be required for formation of the monomeric species.

This result may also be relevant to the amount of catalyst needed for the various asymmetric cyanation reactions. Thus, reactions using trimethylsilyl cyanide are sufficiently enantioselective that they can be carried out at 20 °C.[3] Only 0.1 mol% of the catalyst is needed in these reactions, and at this 'high' temperature this will give rise to a relatively high concentration of monometallic complex **4**. Formation of the monometallic complex is essential to allow it to react with the aldehyde and start the catalytic cycle[4] as shown in Scheme 5. In contrast, reactions using potassium cyanide[8] or ethyl cyanoformate[18] exhibit optimal enantioselectivity at −40 °C. These reactions also require much more catalyst 1–5 mol% and it may be that the reason for this is to maintain the required concentration of monometallic species at the lower temperature.

The dissociation of complex **1** is solvent dependent as in d_6-benzene, a 0.02 M solution of complex **1** exhibited a very



Scheme 5.

simple spectrum consisting of just two imine signals and four aromatic signals as shown in Figure 5. This concentration corresponds to that used for Figure 4b where the signals for the monomeric species were clearly visible. To prove that the species present in d_6-benzene was bimetallic species **1** rather than the monomeric species **4**, a solvent titration was carried out at constant concentration. As the %chloroform in the solvent decreased, the intensity of the minor signals also decreased and they became undetectable when the %chloroform was less than 20%.

Reactions involving catalyst **1** are usually carried out in dichloromethane rather than chloroform or benzene. Therefore, NMR spectra of catalyst **1** were recorded at various concentrations in CD_2Cl_2. The results were very similar to the spectra obtained in $CDCl_3$, with peaks corresponding to monomeric species **4** increasing in intensity as the concentration was reduced. The equilibrium constant in dichloromethane was calculated as 8×10^{-4} M which is a factor of four lower than that observed in chloroform.

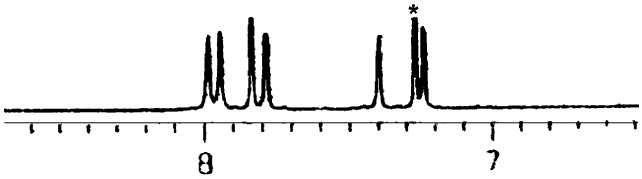


Figure 5. ^{1}H NMR spectrum of compound **1** in C_6D_6 at a concentration of 0.02 M. *Signal due to benzene.

To further prove that the species observed by NMR in $CDCl_3$ were catalytically relevant, the asymmetric addition of potassium cyanide and acetic anhydride to benzaldehyde was carried out under the conditions of Scheme 1 (R^1=Ph, R^2=Me) except that the solvent was changed to chloroform. Under these conditions, an 85% conversion of benzaldehyde into *O*-acetyl (*S*)-mandelonitrile **3a** with 72% enantiomeric excess was observed after a reaction time of 4 days. This reaction is slower and less enantioselective than that carried out under the optimized conditions[8] (93% yield with 90% enantiomeric excess in 10 h), but does prove that the species detected in chloroform are catalytically relevant. The asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1** could also be carried out in chloroform (Table 2: entry 4).

2.5. Mechanistic analysis

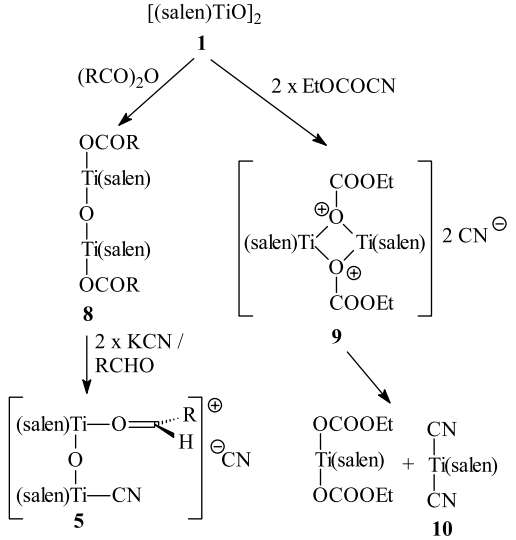
The mechanism shown in Scheme 5 for the addition of trimethylsilyl cyanide to aldehydes catalysed by complex **1** can reasonably be assumed to form the basis of reactions involving ethyl cyanoformate and potassium cyanide/an anhydride as well. There are however, two areas where the mechanism must be modified:

1. How is catalyst **1** converted into one of complexes **5**–**7** present in the catalytic cycle in the absence of trimethylsilyl cyanide?
2. How is the cyanohydrin derivative removed from complex **6**?

We have previously shown[9] that reaction of catalyst **1** with acetic anhydride generates bimetallic *bis*-acetate **8**. Reaction of compound **8** with potassium cyanide and an aldehyde would lead to species **5** as shown in Scheme 6. To start the catalytic cycle when ethyl cyanoformate is used as the cyanide source, it is possible that a complex such as **9** is formed and collapses to titanium *bis*-cyanide complex **10**. This could then enter the catalytic cycle as shown in Scheme 5.

Conversion of complex **6** into *bis*-cyanide **7** in the presence of ethyl cyanoformate presents no difficulty as the ethyl cyanoformate can react with the titanium bound cyanohydrin to give products **2** and complex **7**. In the potassium cyanide/anhydride system however, this step cannot be quite so straightforward. Acylation of the titanium bound cyanohydrin **6** would give products **3** and titanium complex **11** (Scheme 7). Complex **11** could either react with potassium cyanide to give *bis*-cyanide **7**, or directly react with another molecule of aldehyde to reform complex **5**. There is however a further possibility. Since the potassium cyanide chemistry is carried out in the presence of water and *tert*-butanol, complex **6** could be protonated to form a free cyanohydrin and complex **11**. The free cyanohydrin would then be acylated in a non-catalytic step to give the observed product. One consequence of this mechanism is that the enantiomeric excess of product **3** would directly depend on the rate at which the free cyanohydrin was protected by reaction with the anhydride. This fits the observed results since the most reactive anhydrides gave the products with highest enantiomeric excess (acetic anhydride ≥ propionic anhydride > pivalic anhydride > benzoic anhydride). It is also possible that more than one of these routes operate simultaneously, or that the exact process by which the cyanohydrin ester is formed differs from substrate to substrate.

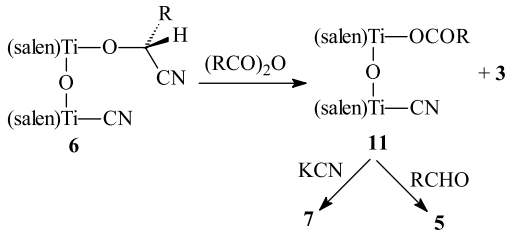
The results of experiments using a sacrificial aldehyde in the potassium cyanide system can be explained as follows. The role of the sacrificial aldehyde is to allow the formation of complex **5** by the route shown in Scheme 6. Complex **5** is one of the three key bimetallic complexes on the catalytic cycle, and its formation appears to take about 4–5 h at −40 °C (based on Fig. 1). During this time, other titanium containing species (e.g., **1**, **4**, **8**) are present in the reaction mixture and could give rise to less enantioselective catalysts resulting in the enantiomeric excess of the product derived from the sacrificial aldehyde being observed to increase with time. Assuming that at least one of complexes **5**–**7** is unstable in the absence of excess aldehyde and therefore causes the partial decomposition of the catalyst prior to the addition of the real substrate, the observed enantiomeric excess of the product derived from the real substrate would be expected to be constant throughout the reaction, but lower than that observed if only one aldehyde was used.



Scheme 6.

3. Conclusions

Catalyst **1** has been shown to catalyse the asymmetric addition of ethyl cyanoformate to a range of aliphatic and aromatic aldehydes. Optimal results were obtained using 5 mol% of catalyst **1** in dichloromethane at −40 °C and under these conditions, twelve aldehydes were converted



Scheme 7.

into (*S*)-cyanohydrin ethyl carbonates with 75–99% enantiomeric excess.

The same catalyst was shown to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of an anhydride, leading to cyanohydrin esters. For this process, only 1 mol% of the catalyst was required and best results were again obtained at −40 °C. Of the anhydrides studied, acetic anhydride generally gave the fastest reaction rates and highest enantioselectivities. Propionic anhydride gave much slower reaction rates, but for aromatic aldehydes gave products with comparable enantiomeric excesses (81–95%) to those obtained using acetic anhydride. When aliphatic aldehydes were used as substrates, the results were more variable and there was no obvious correlation between anhydride structure and enantioselectivity. The other anhydrides studied gave products with significantly lower enantiomeric excesses.

The structure of catalyst **1** was investigated in various solvents to complement a previous X-ray study and to provide mechanistic information. In chloroform, a concentration dependent equilibrium between the dimeric **1** and monometallic **4** forms of the catalyst was detected. In dichloromethane, the equilibrium is shifted in favour of the undissociated form **1**, and in benzene only the undissociated complex is detected. The equilibrium is also temperature dependent, with the monometallic form of the catalyst **4** being less favoured at lower temperatures. These results provide an explanation for the observation that whilst the asymmetric addition of trimethylsilyl cyanide to aldehydes (at room temperature) is catalysed by just 0.1 mol% of catalyst **1**, the corresponding additions of potassium cyanide and ethyl cyanoformate (both of which have to be carried out at −30 to −40 °C to obtain good asymmetric induction) require much larger amounts of catalyst **1**.

For the potassium cyanide system, it was found that the enantiomeric excess of the product increased during the course of the reaction. Experiments in which two different aldehydes were used suggest that this is due to the slow conversion of precatalyst **1** into catalytically active species under the reaction conditions. A complete mechanistic rationale for asymmetric cyanohydrin synthesis (using three different cyanide sources) induced by precatalyst **1** which explains all of the observed effects has been presented.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz, ^{13}C 90 MHz). Variable temperature experiments were carried out on a Bruker Avance 400 Spectrometer, (^{1}H 400 MHz). The solvent for a particular spectrum is given in parentheses. 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), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments.

Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates in the reported solvent, or as KBr disks. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a Bruker Apex III FTMS or Jeol AX505W spectrometer within the chemistry department at King's College. The sample was ionized by electron ionization (EI), chemical ionization (CI) fast atom bombardment (FAB) or electrospray ionization (ES). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 mL).

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 GC was carried out on a Hewlett Packard 5890 gas chromatograph fitted with a thermal conductivity detector, using a γ-CD butyryl, fused silica capillary column (30 m×0.25 mm) and hydrogen as the carrier gas (flow rate 2.3 mL/min).

4.2. General procedure for the asymmetric addition of ethyl cyanoformate to aldehydes

A stirred solution of aldehyde (4.7 mmol) in dichloromethane (20 mL) and (*R*,*R*)-**1** (0.264 g, 0.22 mmol, 5 mol%) was cooled to −84 °C and EtOCOCN (0.93 mL, 9.42 mmol) was added in one portion. The yellow solution was then allowed to warm to −40 °C and was stirred vigorously for 19 h. The reaction mixture was then passed through a pad of silica eluting with dichloromethane. The eluent was concentrated in vacuo and the resulting orange–brown liquid was micro-distilled to give the cyanohydrin ethyl carbonate as a clear liquid.

4.2.1. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 2a. Yield 0.87 g, 90%; $[\alpha]_D^{20}=-20.1$ (*c* 1.8, $CHCl_3$) [lit.[14a] $[\alpha]_D^{20}=+16.2$ (*c* 2.8, $CHCl_3$) for (*R*)-enantiomer with 94% ee]; δ_H 1.26 (3H, t $J=7.1$ Hz, CH_3), 4.2–4.3 (2H, m, OCH_2), 6.19 (1H, s, OCHCN), 7.2–7.5 (5H, m, ArH); δ_C 153.82 (CO_3), 131.64 (ArC), 131.04 (ArCH), 129.68 (ArCH), 128.29 (ArCH), 116.19 (CN), 66.76 (OCH), 66.03 (OCH_2), 14.51 (CH_3); *m*/*z* (EI) 205 (M^+, 35), 116 (78), 133 (55), 105 (100). Found (ES) 206.0829, $C_{11}H_{12}NO_3$ (MH^+) requires 206.0817. GC conditions: initial temperature 100 °C, ramp rate 0.2 °C/min. T_R 121.8 (minor isomer) and 124.2 (major isomer) min.

4.2.2. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile 2b. Yield 1.02 g, 92%; $[\alpha]_D^{20}=+1.8$ (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$) 2981 s, 2845 m, 2250 w, 1753 s, 1611 s, 1580 m, and 1512 cm^{-1} s; δ_H 1.15 (3H, t $J=$ 7.2 Hz, CH_3), 3.76 (3H, s, OCH_3), 4.3–4.4 (2H, m, OCH_2),

6.13 (1H, s, OCHCN), 6.88 (2H, d $J=8.8$ Hz, ArH), 7.41 (2H, d $J=8.8$ Hz, ArH); δ_C 161.73 (CO_3), 153.86 (ArC), 130.11 (ArCH), 123.73 (ArC), 116.34 (CN), 114.97 (ArCH), 66.53 (OCH), 65.86 (OCH_2), 55.82 (OCH_3), 14.50 (CH_3); *m/z* (ES) 253 ($M+NH_4^+$, 15), 146 (100). Found (ES) 253.1186, $C_{12}H_{17}N_2O_4$ ($M+NH_4^+$) requires 253.1183. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 46.3 (major isomer) and 47.3 (minor isomer) min.

4.2.3. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)acetonitrile 2c. Yield 1.04 g, 94%; $[\alpha]_D^{20}=-11.3$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3095 s, 2975 s, 2835 s, 2342 w, and 1755 cm^{-1} s; δ_H 1.38 (3H, t $J=7.1$ Hz, CH_3), 3.86 (3H, s, OCH_3), 4.2–4.3 (2H, m, OCH_2), 6.25 (1H, s, OCHCN), 7.0–7.4 (4H, m, ArH); δ_C 160.53 (CO_3), 153.80 (ArC), 132.92 (ArC), 130.79 (ArCH), 120.36 (ArCH), 116.79 (ArCH), 116.13 (CN), 113.48 (ArCH), 66.64 (OCH), 66.05 (OCH_2), 55.84 (OCH_3), 14.52 (CH_3); *m/z* (EI) 235 (M^+, 30), 146 (100), 134 (93). Found (ES) 236.00902, $C_{12}H_{14}NO_4$ (MH^+) requires 236.0923. GC conditions: initial temperature 100 °C, ramp rate 0.3 °C/min. T_R 174.3 (minor isomer) and 178.6 (major isomer) min.

4.2.4. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methoxyphenyl)acetonitrile 2d. Yield 1.05 g, 95%; $[\alpha]_D^{20}=+57.0$ (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 s, 2839 s, 2508 w, 2248 w, 1760 s, and 1598 cm^{-1} s; δ_H 1.26 (3H, t $J=7.1$ Hz, CH_3), 3.81 (3H, s, OCH_3), 4.2–4.3 (2H, m, OCH_2), 6.51 (1H, s, OCHCN), 6.85 (1H, dd $J=8.3$, 1.6 Hz, ArH), 6.96 (1H, dt $J=8.2$, 1.6 Hz, ArH), 7.38 (1H, dt $J=8.2$, 1.6, Hz, ArH), 7.51 (1H, dd $J=8.2$, 1.6 Hz, ArH); δ_C 157.41 (CO_3), 154.17 (ArC), 132.69 (ArCH), 129.53 (ArCH), 121.63 (ArCH), 120.17 (ArC), 116.58 (CN), 111.75 (ArCH), 66.06 (OCH_2), 62.35 (OCH), 56.04 (OCH_3), 14.79 (CH_3); *m/z* (EI) 235 (M^+, 10), 145 (73), 135 (100), 116 (26), 91 (28). Found (CI) 253.1188, $C_{12}H_{17}N_2O_4$ ($M+NH_4^+$) requires 253.1183. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 163.5 (minor isomer) and 167.6 (major isomer) min.

4.2.5. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methylphenyl)acetonitrile 2e. Yield 0.69 g, 67%; $[\alpha]_D^{20}=-5.1$ (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2986 s, 2874 m, 2247 w, 1756 s, 1616 s, 1576 w, and 1516 cm^{-1} s; δ_H 1.33 (3H, t $J=7.1$ Hz, CH_3), 2.41 (3H, s, CH_3Ar), 4.3–4.4 (2H, m, OCH_2), 6.25 (1H, s, OCHCN), 7.18 (2H, d $J=7.9$ Hz, ArH), 7.45 (2H, d $J=8.2$ Hz, ArH); δ_C 153.86 (CO_3), 141.33 (ArC), 130.30 (ArCH), 128.76 (ArC), 128.31 (ArCH), 116.28 (CN), 66.69 (OCH), 65.91 (OCH_2), 21.70 (CH_3Ar), 14.50 (CH_3CH_2); *m/z* (EI) 219 (M^+, 50), 146 (40), 130 (100), 119 (90), 103 (38), 77 (23). Found (CI) 237.1232, $C_{12}H_{17}N_2O_3$ ($M+NH_4^+$) requires 237.1234. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 109.5 (minor isomer) and 111.1 (major isomer) min.

4.2.6. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)acetonitrile 2f. Yield 1.08 g, 84%; ν_{max} ($CHCl_3$) 2982 m, 2939 m, 2356 w, 1760 s, and 1621 cm^{-1} m; δ_H 1.37 (3H, t $J=7.1$ Hz, CH_3), 4.3–4.4 (2H, m, OCH_2), 6.35 (1H, s, OCHCN), 7.69–7.77 (4H, m, ArH) δ_C 153.61 (CO_3), 135.38 (ArC), 133.05 (q $J=8$ Hz, Ar*C*CF_3), 128.55 (ArCH), 125.39 (q $J=68$ Hz, CF_3), 126.72 (ArCH), 115.51 (CN), 66.71 (OCH_2), 65.86 (OCH), 14.46 (CH_3); *m/z* (EI) 273 (M^+, 18), 201 (100), 173 (99), 134 (35). Found (ES) 274.0674, $C_{12}H_{11}NO_3F_3$ (MH^+) requires 274.0691. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 80.2 (minor isomer) and 83.5 (major isomer) min.

4.2.7. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-chlorophenyl)acetonitrile 2g. Yield 1.08 g, 96%; $[\alpha]_D^{20}=-2.9$ (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3096 m, 3071 m, 2986 s, 2875 m, 2249 w, 1758 s, 1599 s, and 1582 cm^{-1} m; δ_H 1.29 (3H, t $J=7.2$ Hz, CH_3), 4.2–4.3 (2H, m, OCH_2), 6.17 (1H, s, OCHCN), 7.2–7.5 (4H, m, ArH); δ_C 153.68 (CO_3), 137.31 (ArC), 130.17 (ArC), 129.96 (ArCH), 129.65 (ArCH), 115.78 (CN), 66.17 (OCH_2), 66.01 (OCH), 14.49 (CH_3); *m/z* (EI) 241 ((^{37}Cl)M^+, 15), 239 ((^{35}Cl)M^+, 50), 211 (17), 167 (70), 150 (97), 139 (100), 114 (38). Found (ES) 257.0685, $C_{11}H_{14}N_2O_3{}^{35}Cl$ ($M+NH_4^+$) requires 257.0687. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 129.1 (minor isomer) and 131.5 (major isomer) min.

4.2.8. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 2h. Yield 0.51 g, 47%; $[\alpha]_D^{20}=-23.4$ (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3060 m, 2987 s, 2862 m, 2341 w, 2206 w, 1957 w, 1754 s, 1655 m, 1619 m, 1577 m, 1556 m, and 1541 cm^{-1} m; δ_H 1.29 (3H, t $J=7.1$ Hz, CH_3), 4.1–4.2 (2H, m, OCH_2), 5.81 (1H, d $J=6.8$ Hz, OCHCN), 6.14 (1H, dd $J=15.8$, 6.8 Hz, PhCH=C*H*), 6.92 (1H, d $J=15.9$ Hz, PhCH=), 7.2–7.4 (5H, m, ArH); δ_C 153.50 (CO_3), 138.80 (ArCH), 134.67 (ArC), 129.94 (=CH), 129.36 (ArCH), 127.67 (ArCH), 118.25 (=CH), 115.51 (CN), 65.96 (OCH_2), 65.36 (OCH), 14.53 (CH_3); *m/z* (EI) 231 (M^+, 3), 158 (64), 142 (100), 131 (70), 115 (90). Found (ES) 249.1235, $C_{13}H_{17}N_2O_3$ ($M+NH_4^+$) requires 249.1234. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 212.8 (minor isomer) and 220.0 (major isomer) min.

4.2.9. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile 2i. Yield 0.61 g, 54%; $[\alpha]_D^{20}=-66.0$ (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2925 s, 2861 s, 2351 w, and 1756 cm^{-1} s; δ_H 0.90 (3H, t $J=6.8$ Hz, CH_3), 1.36 (3H, t $J=7.2$ Hz, CH_3), 1.3–1.6 (12H, m, $(CH_2)_6$), 1.9–2.0 (2H, m, CH_2), 4.2–4.4 (2H, m, OCH_2), 5.20 (1H, t $J=6.7$ Hz, OCHCN); δ_C 154.01 (CO_3), 116.96 (CN), 65.74 (OCH_2), 65.10 (OCH), 32.75 (CH_2), 32.12 (CH_2), 29.56 (CH_2), 29.43 (CH_2), 29.16 (CH_2), 24.78 (CH_2), 24.98 (CH_2), 14.50 (CH_3), 14.47 (CH_3); *m/z* (CI) 242 (MH^+, 20), 168 (20), 122 (58), 98 (90), 81 (100). Found (ES) 259.2013, $C_{13}H_{27}N_2O_3$ ($M+NH_4^+$) requires 259.2016. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 101.3 (minor isomer) and 103.1 (major isomer) min.

4.2.10. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3-methyl-butanonitrile 2j. Yield 0.18 g, 23%; $[\alpha]_D^{20}=-59.8$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 m, 2881 m, 2236 w, and 1758 cm^{-1} s; δ_H 1.1–1.2 (6H, m, $(CH_3)_2$), 1.34 (3H, t $J=7.2$ Hz, CH_3CH$_2$), 2.1–2.2 (1H, m, $CHMe_2$), 4.3–4.4 (2H, m, OCH_2), 5.05 (1H, d $J=5.8$ Hz, OCHCN); δ_C 154.12 (CO_3), 116.05 (CN), 70.36 (OCH), 65.75 (OCH_2), 31.61 (Me_2CH), 18.04 (CH_3CH), 17.65 (CH_3CH), 14.50 (CH_3CH$_2$); *m/z* (ES) 172 (MH^+, 100), 145 (7), 128 (6),

82 (13), 57 (33). Found (CI) 189.1229, $C_8H_{17}N_2O_3$ ($M+NH_4^+$) requires 189.1234. GC conditions: initial temperature 60 °C, ramp rate 5.0 °C/min. T_R 16.1 (minor isomer) and 16.2 (major isomer) min.

4.2.11. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexyl-ethanonitrile 2k. Yield 0.81 g, 82%; $[\alpha]_D^{20}=-32.2$ (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 2934 s, 2857 s, 2245 m, and 1756 cm^{-1} s; δ_H 1.2–1.3 (6H, m, $(CH_2)_3$), 1.33 (3H, t $J=7.2$ Hz, CH_3), 1.7–2.0 (5H, m, CH_2CHCH_2), 4.2–4.3 (2H, m, OCH_2), 5.04 (1H, d $J=5.8$ Hz, OCHCN); δ_C 154.16 (CO_3), 116.21 (CN), 69.63 (OCH), 65.71 (OCH_2), 40.52 (CH), 28.34 (CH_2), 28.16 (CH_2), 26.06 (CH_2), 25.68 (CH_2), 25.60 (CH_2), 14.49 (CH_3); *m/z* (CI) 212 (MH^+, 100), 129 (46), 95 (33), 83 (79), 55 (90). Found (CI) 229.1548, $C_{11}H_{21}N_2O_3$ ($M+NH_4^+$) requires 229.1547. GC conditions: initial temperature 60 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 274.0 (minor isomer) and 276.4 (major isomer) min.

4.2.12. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 2l. Yield 0.60 g, 69%; $[\alpha]_D^{20}=-48.5$ (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 s, 2237 w, and 1754 cm^{-1} s; δ_H 1.05 (9H, s, $C(CH_3)_3$), 1.26 (3H, t $J=7.1$ Hz, CH_3CH_2), 4.2–4.3 (2H, m, OCH_2), 4.85 (1H, s, OCHCN); δ_C 151.32 (CO_3), 116.14 (CN), 73.57 (OCH), 65.65 (OCH_2), 35.27 (CMe_3), 25.48 (CH_3CH_2), 14.51 ($C(CH_3)_3$); *m/z* (CI) 186 (MH^+, 88), 96 (43), 57 (100), 41 (49). Found (CI) 203.1396, $C_9H_{19}N_2O_3$ ($M+NH_4^+$) requires 203.1390. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 13.9 (minor isomer) and 14.2 (major isomer) min.

4.3. General procedure for the asymmetric addition of potassium cyanide and an anhydride to aldehydes

To a stirred mixture, cooled at −90 °C, of KCN (2.54 g, 39.2 mmol) and catalyst **1** (118 mg, 0.098 mmol) in dry dichloromethane (20 mL), *t*-BuOH (0.98 mL, 10.3 mmol), water (0.1 mL, 4.4 mmol), aldehyde (9.8 mmol) and anhydride (39.2 mmol) were added. The reaction was warmed to −40 °C, monitored by chiral GC at suitable intervals and allowed to stir until the reaction was >90% complete. Solid salts were filtered and washed thoroughly with dichloromethane. The filtrate was passed through a pad of silica (10 mm×50 mm) eluting with dichloromethane to remove catalyst **1**. The solvent was evaporated in vacuo, and the residue purified by distillation or flash chromatography (ethyl acetate/hexane 1/5) to give the (*S*)-cyanohydrin ester.

4.3.1. *O*-Propanoyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3b.[23a] Yield 99%; $[\alpha]_D^{25}-5.09$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2987 m, and 1756 cm^{-1} s; δ_H 1.20 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.62 (1H, s, CH), 7.4–7.6 (5H, m, ArH); δ_C 170.67 (CO_2), 131.29 (ArC), 129.69 (ArCH), 128.59 (ArCH), 127.16 (ArCH), 115.65 (CN), 62.13 (OCH), 26.70 (CH_2), 7.70 (CH_3); *m/z* (EI) 189 (M^+, 15), 133 (30), 116 (34), 57 (100)). Found (ES) 212.0685, $C_{11}H_{11}NO_2Na$ ($M+Na^+$) requires 212.0685. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 14.5 (minor isomer) and 14.9 (major isomer) min.

4.3.2. *O*-Pivaloyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3c.[24a] Yield 85%; $[\alpha]_D^{25}-1.1$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2978 s, 1809 m, and 1742 cm^{-1} s; δ_H 1.26 (9H, s, $(CH_3)_3$), 6.40 (1H, s, CH), 7.4–7.6 (5H, m ArCH); δ_C 174.25 (CO_2), 132.43 (ArC), 130.54 (ArCH), 129.55 (ArCH), 127.80 (ArCH), 116.61 (CN), 63.14 (OCH), 40.49 (C), 26.94 (CH_3); *m/z* (EI) 217 (M^+, 75), 116 (68), 57 (100). Found (ES) 240.0996, $C_{13}H_{15}NO_2Na$ ($M+Na^+$) requires 240.1000. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.4 °C/min. T_R 18.6 (minor isomer) and 18.8 (major isomer) min.

4.3.3. *O*-Benzoyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3d.[25a] Yield 98%; $[\alpha]_D^{25}-9.3$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 3065 m, 1785 s, and 1598 cm^{-1} s; δ_H 6.61 (1H, s, CH), 7.3–7.4 (6H, m, ArH), 7.5–7.6 (2H, m, ArH), 8.0–8.0 (2H, m, ArH); δ_C 162.78 (CO_2), 135.30 (ArC), 134.99 (ArC), 131.32 (ArCH), 130.68 (ArCH), 129.32 (ArCH), 128.98 (ArCH), 128.27 (ArCH), 116.68 (CN), 63.80 (OCH), *m/z* (ES) 475 ($2M+H^+$, 55), 411 (15), 260 ($M+Na^+$, 40), 249 (100). Found (ES) 238.0873, $C_{15}H_{12}NO_2$ (MH^+) requires 238.0868. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 17.3 (minor isomer) and 18.0 (major isomer) min.

4.3.4. *O*-Propanoyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 3e. Yield 62%; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2989 m, and 1760 cm^{-1} s; δ_H 1.11 (3H, t $J=7.3$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.06 (1H, d $J=7.5$ Hz, CHCN), 6.17 (1H, dd $J=15.8$, 6.7 Hz, PhCH=CH), 6.96 (1H, d $J=15.8$ Hz, PhCH=), 7.2–7.5 (5H, m, ArH); δ_C 172.84 (CO_2), 138.15 (ArC), 134.83 (=CH), 129.78 (ArCH), 129.24 (ArCH), 127.57 (ArCH), 118.87 (=CH), 116.00 (CN), 61.81 (OCH), 27.54 (CH_2), 9.15 (CH_3); *m/z* (EI) 215 (M^+, 14), 159 (51), 141 (93), 115 (100), 57 (74). Found (ES) 238.0911, $C_{13}H_{13}NO_2Na$ ($M+Na^+$) requires 238.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 2.0 °C/min. T_R 43.0 (minor isomer) and 44.9 (major isomer) min.

4.3.5. *O*-Pivaloyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 3f. Yield 50%; $[\alpha]_D^{25}+10.1$ (*c* 4.0, $CHCl_3$), ν_{max} (neat) 2976 s, 1744 s, and 1480 cm^{-1} s; δ_H 1.19 (9H, s, $(CH_3)_3$), 5.94 (1H, d *?*=6.7 Hz, CHCN), 6.12 (1H, dd $J=15.8$, 6.7 Hz, PhCH=CH), 6.89 (1H, d $J=15.8$ Hz, PhCH=), 7.2–7.4 (5H, m, ArH); δ_C 176.89 (CO_2), 138.03 (=CH), 134.87 (ArC), 129.77 (ArCH), 129.24 (ArCH), 127.58 (ArCH), 118.90 (=CH), 116.05 (CN), 61.92 (OCH), 39.30 (CMe_3), 27.30 (CH_3); *m/z* (ES) 509 ($2M+Na^+$, 12), 488 (31), 467 (36), 266 ($M+Na^+$, 85), 245 (100), 223 (67), 209 (45), 142 (85). Found (ES) 509.2430 and 266.1148, $C_{30}H_{34}N_2O_4Na$ ($2M+Na^+$) requires 509.2416, $C_{15}H_{17}NO_2Na$ ($M+Na^+$) requires 266.1157. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 25.5 (minor isomer) and 25.7 (major isomer) min.

4.3.6. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-trifluoromethyl-phenyl)-acetonitrile 3g. Yield 99%; $[\alpha]_D^{25}-1.1$ (*c* 12.0, $CHCl_3$); ν_{max} (neat) 2989 m, and 1760 cm^{-1} s; δ_H 1.16 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.45 (1H, s, CH), 6.6–7.7 (4H, m, ArH); δ_C 172.64 (CO_2), 135.99

(ArC), 132.70 (q $J=33$ Hz, CF_3), 126.69 (ArCH), 125.41 (ArCH), 116.00 (CN), 62.39 (OCH), 27.47 (CH_2), 9.08 (CH_3); *m/z* (EI) 257 (M^+, 25), 238 (30), 201 (75), 184 (80), 57 (100). Found (ES) 280.0555, $C_{12}H_{10}NO_2F_3Na$ ($M+Na^+$) requires 280.0551. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 3.0 °C/min. T_R 21.2 (minor isomer) and 22.0 (major isomer) min.

4.3.7. *O*-Pivaloyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)-acetonitrile 3h. Yield 99%; $[\alpha]_D^{25}-5.4$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 2979 s, 1808 m, and 1749 cm^{-1} s; δ_H 1.29 (9H, s, $(CH_3)_3$), 6.48 (1H, s, CH), 7.66 (2H, d $J=8.3$ Hz, ArCH), 7.74 (2H, d $J=8.3$ Hz ArCH); δ_C 175.31 (CO_2), 136.19 (ArC), 132.99 (q $J=33$ Hz, CF_3), 128.25 (ArC), 126.72 (ArCH), 122.41 (ArCH), 116.02 (CN), 62.46 (OCH), 39.29 (C), 27.18 (CH_3); *m/z* (ES) 308 ($M+Na^+$, 100), 184 (40). Found (ES) 308.0867, $C_{14}H_{14}NO_2F_3Na$ ($M+Na^+$) requires 308.0869. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.4 °C/min. T_R 21.3 (minor isomer) and 21.6 (major isomer) min.

4.3.8. *O*-Propanoyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)-acetonitrile 3j. Yield 87%; $[\alpha]_D^{25}-2.1$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2984 m, 2945 m, and 1754 cm^{-1} s; δ_H 1.19 (3H, t $J=7.6$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 3.84 (s, 3H, OCH_3), 6.40 (1H, s, CH), 7.0–7.4 (4H, m, ArH); δ_C 172.80 (CO_2), 160.49 (ArC), 133.58 (ArC), 130.74 (ArCH), 120.58 (ArCH), 116.60 (ArCH), 116.31 (CN), 113.61 (ArCH), 62.99 (OCH), 55.81 (OCH_3), 27.51 (CH_2), 9.14 (CH_3); *m/z* (EI): 219 (M^+, 42), 163 (100), 146 (39), 57 (34). Found (ES) 242.0787, $C_{12}H_{13}NO_3Na$ ($M+Na^+$) requires 242.0782. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 15.1 (minor isomer) and 15.3 (major isomer) min.

4.3.9. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)-acetonitrile 3l. Yield 71%; $[\alpha]_D^{25}+12.7$ (*c* 11.4, $CHCl_3$); ν_{max} (neat) 3022 w, 2944 m, and 1752 cm^{-1} s; δ_H 1.23 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 3.89 (3H, s, OCH_3), 6.43 (1H, s, CH), 6.9–7.0 (2H, m, ArH), 7.4–7.5 (2H, m, ArH); δ_C 172.82 (CO_2), 160.48 (ArC), 133.57 (ArC), 130.75 (ArCH), 120.28 (ArCH), 116.62 (CN), 63.01 (OCH), 55.82 (OCH_3), 27.52 (CH_2), 9.14 (CH_3); *m/z* (EI) 219 (M^+, 32), 163 (35), 146 (100). Found (ES) 242.0783, $C_{12}H_{13}NO_3Na$ ($M+Na^+$) requires 242.0782. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.9 (minor isomer) and 17.3 (major isomer) min.

4.3.10. *O*-Propanoyl (*S*)-2-hydroxy-3-methyl-butanonitrile 3n.[23a] Yield 99%; $[\alpha]_D^{25}+3.0$ (*c* 5.0, $CHCl_3$); ν_{max} (neat) 2970 s, 2879 s, and 1754 cm^{-1} s; δ_H 1.07 (6H, d $J=6.8$ Hz, $(CH_3)_2CH$), 1.17 (3H, t $J=7.6$ Hz, CH_3CH_2), 2.1–2.2 (1H, m, $CHMe_2$), 2.3–2.5 (2H, m, CH_2CH_3), 5.17 (1H, d $J=5.8$ Hz, OCH); δ_C 173.03 (CO_2), 116.48 (CN), 66.55 (OCH), 31.44 (CH), 27.43 (CH_2), 18.12 (CH_3), 17.73 (CH_3), 9.17 (CH_3); *m/z* (CI) 156 (MH^+, 26), 57 (100). GC conditions: initial temperature 60 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 14.1 (minor isomer) and 14.5 (major isomer) min.

4.3.11. *O*-Propanoyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 3p. Yield 99%; $[\alpha]_D^{25}-3.8$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 2971 s, 2878 s, and 1754 cm^{-1} s; δ_H 1.09 (9H, s, $(CH_3)_3$), 1.18 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.38 (2H, q $J=7.6$ Hz, CH_3CH_2), 5.07 (1H, s, OCH); δ_C 171.59 (CO_2), 116.56 (CN), 69.59 (OCH), 35.08 (CMe_3), 32.84 (CH_2), 25.60 (CH_3), 8.42 (CH_3); *m/z* (CI) 170 (MH^+, 42), 113 (15), 57 (100). GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 20.7 (minor isomer) and 21.2 (major isomer) min.

4.3.12. *O*-Propanoyl (*S*)-2-hydroxy-2-(2-methylphenyl)-acetonitrile 3q. Yield 99%; $[\alpha]_D^{25}-13.0$ (*c* 6.0, $CHCl_3$); ν_{max} (neat) 2984 m, and 1753 cm^{-1} s; δ_H 1.23 (3H, t $J=7.4$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 2.45 (3H, s, CH_3Ar), 6.55 (1H, s, OCH), 7.2–7.4 (3H, m, ArH), 7.5–7.6 (1H, m, ArH); δ_C 172.78 (CO_2), 137.05 (ArC), 131.70 (ArC), 130.83 (ArCH), 130.36 (ArCH), 128.89 (ArCH), 127.18 (ArCH), 116.49 (CN), 61.34 (OCH), 27.40 (CH_2), 19.29 ($ArCH_3$), 9.16 (CH_3); *m/z* (EI) 203 (M^+, 10), 129 (100), 103 (48). Found (ES) 226.0837, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 19.4 (minor isomer) and 19.9 (major isomer) min.

4.3.13. *O*-Propanoyl (*S*)-2-hydroxy-2-(3-methylphenyl)-acetonitrile 3r. Yield 98%; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2985 m, 2945 m, and 1753 cm^{-1} s; δ_H 1.26 (3H, t $J=5.9$ Hz, CH_2CH_3), 2.32 (3H, s, CH_3Ar), 2.4–2.5 (2H, m, CH_2CH_3), 6.32 (1H, s, OCH), 7.2–7.3 (4H, m, ArH); δ_C 172.84 (CO_2), 139.60 (ArC), 132.21 (ArC), 131.49 (ArCH), 129.51 (ArCH), 128.81 (ArCH), 122.30 (ArCH), 116.49 (CN), 61.18 (OCH), 27.53 (CH_2), 21.72 ($ArCH_3$), 9.14 (CH_3); *m/z* (ES) 226 ($M+Na^+$, 100). Found (ES) 226.0837, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.3 (minor isomer) and 16.5 (major isomer) min.

4.3.14. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-methylphenyl)-acetonitrile 3s. Yield 98%; $[\alpha]_D^{25}+3.5$ (*c* 6.0, $CHCl_3$); ν_{max} (neat) 2985 m, 2845 m, and 1755 cm^{-1} s; δ_H 1.18 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.15 (3H, s, CH_3Ar), 2.3–2.5 (2H, m, CH_2), 6.40 (1H, s, CHO), 7.26 (2H, d $J=8.0$ Hz, ArCH), 7.46 (2H, d $J=8.1$ Hz, ArCH); δ_C 172.87 (CO_2), 140.99 (ArC), 130.26 (ArC), 129.39 (ArCH), 128.20 (ArCH), 116.79 (CN), 63.05 (OCH), 27.51 (CH_2), 21.65 ($ArCH_3$), 9.10 (CH_3); *m/z* (ES) 226 ($M+Na^+$, 100), 130 (22). Found (ES) 226.0790, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.4 (minor isomer) and 16.6 (major isomer) min.

4.3.15. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-chlorophenyl)-acetonitrile 3t. Yield 99%; $[\alpha]_D^{25}+13.3$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2986 s, 2945 s, and 1754 cm^{-1} s; δ_H 1.15 (3H, t $J=7.4$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.37 (1H, s, OCH), 7.4–7.5 (4H, m, ArH); δ_C 172.72 (CO_2), 136.99 (ArC), 130.79 (ArC), 129.91 (ArCH), 129.61 (ArCH), 116.24 (CN), 62.43 (OCH), 27.49 (CH_2), 9.22 (CH_3); *m/z* (EI) 225 (($^{37}Cl)M^+$, 18), 223 (($^{35}Cl)M^+$, 51), 150 (100), 57 (90). Found (ES) 246.0293, $C_{11}H_{10}NO_2^{35}ClNa$ (($^{35}Cl)M+$

Na^+) requires 246.0230. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 21.9 (minor isomer) and 23.0 (major isomer) min.

4.3.16. *O*-Propanoyl (*S*)-2-hydroxy-decanonitrile 3u. Yield 74%; $[\alpha]_D^{25}$ −3.7 (*c* 10.6, $CHCl_3$); ν_{max} (neat) 2928 s, 2850 m, and 1752 cm^{-1} s; δ_H 0.88 (3H, t J=7.1 Hz, $CH_3(CH_2)_7$), 1.19 (3H, t J=7.5 Hz, CH_2CH_3), 1.30–1.32 (12H, m, $(CH_2)_6$), 1.9–2.0 (2H, m, CH_2CH), 2.4–2.5 (2H, m, CH_2CO), 5.34 (1H, t J=6.8 Hz, OCH); δ_C 173.06 (CO_2), 117.44 (CN), 61.37 (OCH), 32.71 (CH_2), 32.15 (CH_2), 29.47 (CH_2), 29.19 (CH_2), 27.48 (CH_2), 24.92 (CH_2), 23.01 (CH_2), 17.73 (CH_2), 14.45 (CH_3), 9.16 (CH_3); *m/z* (CI) 226 (MH^+, 24), 81 (51), 57 (100). Found (ES) 248.1617, $C_{13}H_{23}NO_2Na$ ($M+Na^+$) requires 248.1628. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.6 (minor isomer) and 17.2 (major isomer) min.

4.3.17. *O*-Propanoyl (*S*)-2-hydroxy-2-cyclohexyl-acetonitrile 3v.[23a] Yield 95%; $[\alpha]_D^{25}$ −7.5 (*c* 13.6, $CHCl_3$); ν_{max} (neat) 3025 w, 2931 m, 1813 m, and 1752 cm^{-1} s; δ_H 1.19 (3H, t J=7.4 Hz, CH_3), 1.1–1.4 (6H, m, $(CH_2)_3$), 1.7–2.0 (4H, m, (CH_2CHCH_2), 2.4–2.5 (3H, m, $CH(CH_2)_2+CH_3CH_2$), 5.20 (1H, d J=6.0 Hz, OC*H*); δ_C 170.84 (CO_2), 116.61 (CN), 65.73 (OCH), 40.30 (CH), 29.06 (CH_2), 28.69 (CH_2), 28.40 (CH_2), 27.01 (CH_2), 26.35 (CH_2), 25.61 (CH_2), 9.09 (CH_3); *m/z* (CI) 196 (MH^+, 80), 113 (45), 57 (100). GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.7 (minor isomer) and 16.9 (major isomer) min.

4.4. General procedure for the use of a sacrificial aldehyde

To a stirred mixture, cooled to −40 °C, of KCN (2.54 g, 39.21 mmol), complex **1** (9 mg, 0.098 mmol), *t*-BuOH (0.098 mL, 10.3 mmol) and water (0.1 mL, 4.4 mmol), in dry dichloromethane (20 mL), the sacrificial aldehyde (2 or 10 mol%, 0.16 mmol or 0.83 mmol) and propionic anhydride (5.03 mL, 39.3 mmol) were added. The reaction was left for 3–5 h at −40 °C and monitored by GC chiral analysis. The real aldehyde (90 or 98 mol%, 8.5 or 9.25 mmol) was then added and the reaction was monitored by TLC (ethyl acetate/hexane) and chiral GC (for both aldehydes) until the reaction was complete (ca 48 h). The reaction was warmed to room temperature; solids were removed by filtration and washed thoroughly with dichloromethane. To remove the catalyst, the filtrate was passed through a pad of silica (10 mm×50 mm) eluting with dichloromethane. The solvent was evaporated in vacuo, and the resulting yellowish residue purified by flash chromatography (ethyl acetate/hexane) or distillation.

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