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Enantioselective and diastereoselective syntheses of cyanohydrin carbonates

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Abstract—A new and general synthesis of alkyl cyanoformates is presented starting from the appropriate alcohol and oxalyl chloride. This is used to prepare enantiomerically pure cyanoformates from enantiomerically pure primary and secondary alcohols. Optimal conditions for the addition of various achiral cyanoformates to aldehydes catalysed by an enantiomerically pure titanium(salen) catalyst in the presence of potassium cyanide as a cocatalyst are developed. Under these conditions, two chiral cyanoformates also reacted with aldehydes to give cyanohydrin carbonates. The stereochemistry of this process is predominantly determined by the stereochemistry of the titanium(salen) catalyst and the stereochemistry of two of the cyanohydrin carbonates was confirmed by X-ray crystallography. In a further extension of the chemistry, a homogeneous system in which the potassium cyanide/18-crown-6 complex is used as the cyanide cocatalyst has been developed and the kinetics of this reaction show that it displays first order kinetics, provided at least 2 mol % of the potassium cyanide complex are employed.

1. Introduction

One of the success stories in asymmetric catalysis over the last decade has been the development of effective catalysts for the asymmetric addition of cyanide to aldehydes and ketones.[1,2] Ten years ago, this simple asymmetric carbon–carbon bond forming reaction could only be accomplished using volatile cyanide sources (hydrogen cyanide or trimethylsilyl cyanide); reactions using synthetic catalysts typically required the use of 20–100 mol % of catalyst at low temperature (typically −20 to −80 °C) and reaction times in excess of 100 h were not uncommon.[3] Whilst nature had provided a family of oxynitrilase enzymes to accomplish the same transformation, these required the use of hydrogen cyanide, and were often difficult to isolate (with the notable exception of the oxynitrilase from almonds) and had a narrow substrate range, especially with regard to the use of ketones as substrates.[4]

The various problems associated with asymmetric cyanohydrin synthesis have now largely been solved by advances made by a number of groups. The three most effective classes of catalysts for the asymmetric addition of trimethylsilyl cyanide to carbonyl compounds developed to date are our titanium[5,6] and vanadium[6–9] based salen complexes **1** and **2**, aluminium complexes **3** and **4** of binol functionalised with additional Lewis bases developed by Shibasaki et al.[10] and Nájera et al.,[11] respectively, and complexes of titanium and lanthanide metals with glucose derived chiral ligands **5** also discovered by Shibasaki et al.[12] Of these, complexes **1** and **2** have the advantages of being active at very high substrate to catalyst ratios (1000:1) and give cyanohydrin trimethylsilyl ethers derived from aldehydes with good enantiomeric excesses at room temperature. As a result, they have been widely adopted by other research groups[13,14] and oligomeric, ionic liquid soluble[15] and insolubilised versions of the catalysts have been developed.[16] Complexes **3** and **4** have been used to prepare cyanohydrin trimethylsilyl ethers with even higher enantiomeric excesses, though at lower temperatures and using lower substrate to catalyst ratios. Metal complexes of ligands **5** give especially good results in the addition of trimethylsilyl cyanide to ketones.

The availability of effective catalysts for asymmetric cyanohydrin synthesis along with a mechanistic understanding of their mode of action has opened up the possibility of using other, more convenient cyanide sources for asymmetric cyanohydrin synthesis as trimethylsilyl cyanide is both volatile and expensive. Catalysts **1** and **2** (along with polymer supported versions of these complexes[16]) are unique in that

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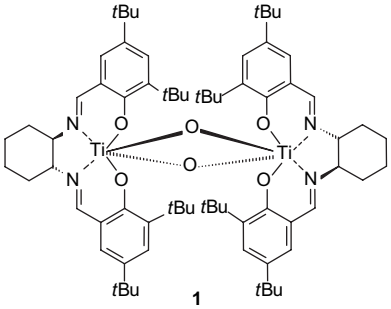

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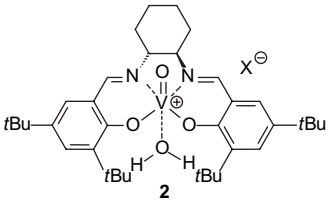

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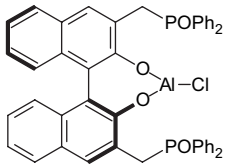

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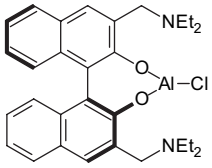

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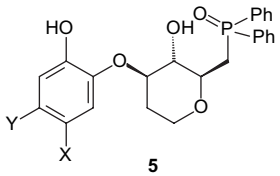

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they are compatible with potassium cyanide in the presence of an anhydride, thus allowing the direct asymmetric synthesis of cyanohydrin esters.[17,18] Complex **1** can also be used with acyl cyanides to achieve the same transformation under homogeneous reaction conditions.[19] Similarly, the titanium analogue of complex **4** has been shown to catalyse the asymmetric addition of benzoyl cyanide to aldehydes.[20] Complex **4** has also been shown to accept diethyl cyanophosphonate as a cyanide source,[21,22] thus allowing the direct asymmetric synthesis of cyanohydrin phosphonates.[23]

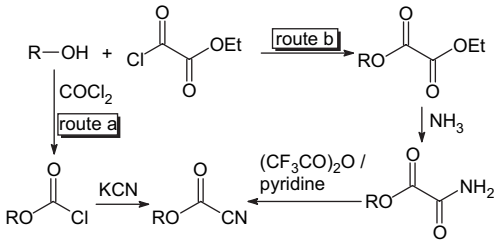
However, the most popular alternatives to trimethylsilyl cyanide are simple alkyl cyanoformates since cyanohydrin carbonates are configurationally stable and significantly less prone to hydrolysis than cyanohydrin trimethethylsilyl ethers and the addition of cyanoformates to carbonyl compounds is 100% atom economical. Complex **1** (but not vanadium based complex **2**) will catalyse the asymmetric addition of ethyl cyanoformate to aldehydes,[18,19,24] and we have demonstrated that this process is cocatalysed by cyanide ions, allowing a wider range of cyanoformates to be utilised.[25] Recently, an in situ prepared complex derived from a salen ligand and titanium tetra-isopropoxide has also been shown to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes in the presence of excess isopropanol.[26] Complex **4** has been shown to accept methyl cyanoformate[22,27] as the cyanide source. A variety of other chiral Lewis acids[28] and Lewis bases[29] have also been shown to catalyse the asymmetric addition of alkyl cyanoformates to aldehydes and ketones. Additionally, there is one report of an enzymatic synthesis of cyanohydrin carbonates,[30] and aluminium(salen) complexes have been used to catalyse the asymmetric addition of cyanoformates to acylsilanes with concomitant Brook rearrangement.[31]

In this manuscript, we give full details of our recently disclosed[25] enantioselective and diastereoselective syntheses of cyanohydrin carbonates using achiral and chiral cyanoformates, respectively. The mechanism of these reactions has been probed by studying the reaction kinetics. In addition, an improved route for the synthesis of alkyl cyanoformates is presented, and the relative stereochemistry of two of the cyanohydrin carbonates is rigorously established by X-ray crystallography.

2. Results and discussion

2.1. Synthesis of enantiomerically pure cyanoformates

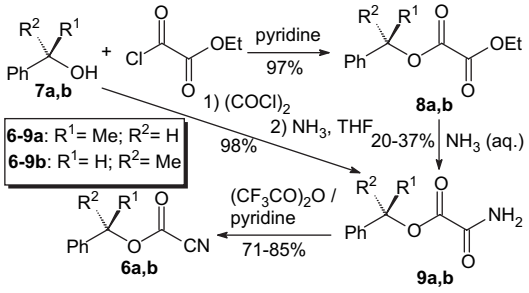
Cyanoformates can be synthesised from alcohols by two main routes[32] as shown in Scheme 1. Treatment of an alcohol with excess phosgene followed by potassium cyanide in the presence of 18-crown-6 (route a) provides the most direct route and has been used to prepare a range of aliphatic cyanoformates.[33] An alternative process was developed for the synthesis of *tert*-butyl cyanoformate (route b).[34] Thus, reaction of *tert*-butanol with ethyl oxalyl chloride provides a mixed oxalic diester. Ammonolysis of the less hindered ethyl ester then provides an oxamide, which can be dehydrated to the desired cyanoformate.



Scheme 1.

Initially, 1-phenylethanol was selected as a suitable chiral alcohol as the racemate and both enantiomers are commercially available and the phenyl and methyl groups have significantly different steric and electronic properties, which should be advantageous for subsequent diastereoselective reactions with aldehydes. The corresponding cyanoformate **6** was not a known compound, and all attempts to prepare it by route a shown in Scheme 1 were unsuccessful. The intermediate 1-phenylethyl chloroformate was found to rapidly decompose to 1-phenylethyl chloride, presumably by an S_N1 type process due to the relative stability of the secondary, benzylic carbenium ion. Therefore, the synthesis of compound **6** by route b was investigated (Scheme 2). Reaction between (*R*)- or (*S*)-1-phenylethanol **7a**,**b** and ethyl oxalyl chloride proceeded smoothly to give the desired mixed diesters **8a**,**b** in 97% yield. However, the subsequent reaction between diesters **8a**,**b** and ammonia was problematic. The reaction appeared not to be as selective as observed for ethyl

tert-butyl oxalate, and gave a mixture of the desired 1-phenylethyl oxamides **9a**,**b**, ethyl oxamide, oxamide and recovered 1-phenylethanol. Whilst it was possible to isolate pure samples of oxamides **9a**,**b** from this reaction, this required repeated slow recrystallisations and resulted in low and inconsistent yields (20–37%) of oxamides **9a**,**b**. Nevertheless, gram quantities of oxamides **9a**,**b** could be accessed by this route, and the subsequent dehydration of these amides to the desired cyanoformates **6a**,**b** was straightforward. Cyanoformates **6a**,**b** were isolated as colourless oils in 71–85% yield.



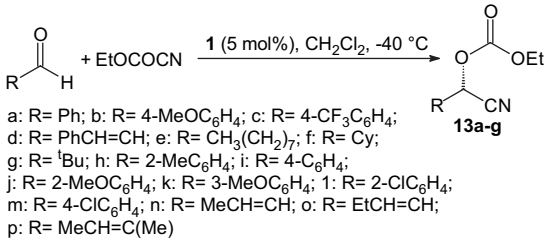
Scheme 2.

To avoid the problems associated with the ammonolysis of diesters **8**, an alternative synthesis of amides **9** was developed. Thus, treatment of alcohol **7b** with 2 equiv of oxalyl chloride gave (*S*)-1-phenylethyl oxalyl chloride,[35] which was immediately reacted with a solution of ammonia in THF to provide amide **9b** in 98% yield as shown in Scheme 2.

The optimised synthesis of cyanoformates shown in Scheme 2 was used to prepare four other enantiomerically pure cyanoformates **10a**,**d** derived from commercially available, enantiomerically pure alcohols **11a**,**d** as shown in Scheme 3. For ethyl lactate **11a** and ethyl mandelate **11b**, high yields of the oxamides **12a**,**b** could only be obtained if the alcohol was deprotonated with sodium hydride prior to the addition of oxalyl chloride.[36] In contrast, menthol and glycerol acetonide were converted into oxamides **12c**,**d** in good yields without the need for prior deprotonation of the alcohol.[37] Amides **12a–c** were subsequently converted into cyanoformates **10a–c** in high yield.[38] However, oxamide **12d** gave only a low yield of cyanoformate **10d**, which is probably due to the acid and thermal sensitivity of the acetonide protecting group, combined with the hydrophilic nature of compound **10d**.

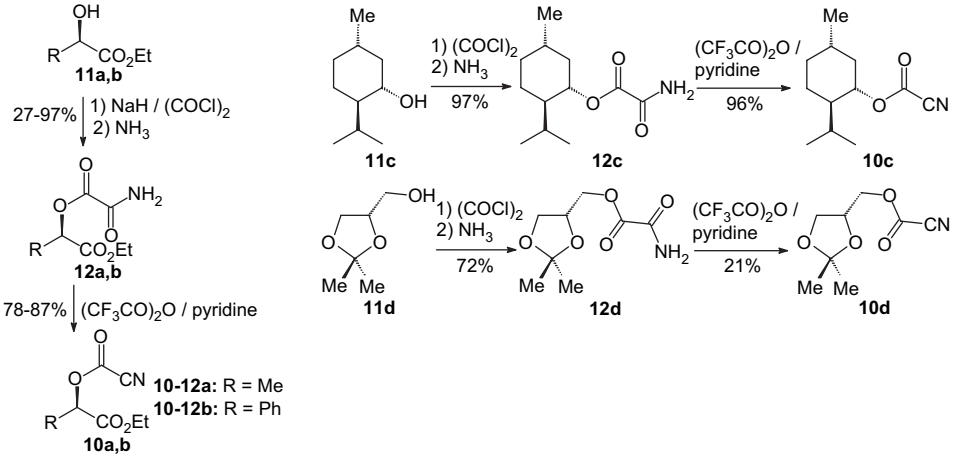
2.2. Cyanide ion cocatalysis in the asymmetric synthesis of cyanohydrin carbonates from achiral cyanoformates

Catalyst **1** is capable of catalysing the asymmetric addition of ethyl cyanoformate to aldehydes,[18,19,24] giving non-racemic cyanohydrin ethyl carbonates **13** as shown in Scheme 4. However, this process requires a relatively large amount of catalyst (5 mol %), and preliminary studies showed that more hindered achiral or chiral cyanoformates were not the substrates for this reaction. Therefore, we embarked on a study to optimise the reaction conditions for complex **1** catalysed cyanohydrin carbonate synthesis so as to allow the use of a wide variety of cyanoformates.



Scheme 4.

A study of the kinetics of this reaction (see Section 2.5) showed that the reaction between benzaldehyde and ethyl cyanoformate catalysed by complex **1** could not be fitted to any simple reaction order (zero to third). This was in contrast to the reactions involving catalyst **1** and trimethylsilyl cyanide, which always obey first order kinetics.[5b,6] In view of these kinetic results, it seemed likely that ethyl cyanoformate may be hydrolysed to cyanide ion in situ and that cyanide was the actual cyanating agent in these reactions. The concentration of cyanide would hence increase as the reaction progressed, thus accounting for the non-linear kinetics observed. Trapping of the so-formed cyanohydrin alkoxide by another molecule of ethyl cyanoformate would then produce cyanohydrin ethyl carbonate **13** and regenerate cyanide



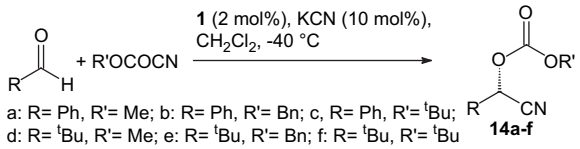
Scheme 3.

ion. Therefore, it was felt that adding additional cyanide ions to these reactions might increase the rate of reaction, and thus allow the amount of catalyst **1** to be reduced and/or allow other less reactive cyanoformates to be used.

An initial reaction using benzaldehyde, complex **1** (2 mol %) and tetrabutylammonium cyanide (5 mol %) as cocatalyst was not encouraging since mandelonitrile ethyl carbonate (**13**, R=Ph) was obtained with just 4% enantiomeric excess. However, this reaction had gone to completion after 24 h, despite the reduced amount of complex **1** used. Fortunately, changing the cyanide source to potassium cyanide restored the enantioselectivity, whilst retaining the accelerated rate of reaction.[39] Selected results for the addition of ethyl cyanoformate (1.2 equiv) to benzaldehyde in dichloromethane catalysed by complex **1** and potassium cyanide are summarised in Table 1.

Entries 1 and 2 of Table 1 confirm that in the absence of potassium cyanide, complete conversion of benzaldehyde to mandelonitrile ethyl carbonate **13** requires 5 mol % of catalyst **1**, with negligible reaction occurring when just 1 mol % of catalyst was used even at room temperature over an extended reaction time. Comparison of entries 2 and 3 of Table 1 clearly demonstrates the catalytic effect of potassium cyanide on this reaction, though at room temperature the asymmetric induction is rather low. Increasing the amount of potassium cyanide catalyst at room temperature (Table 1: entry 4) did increase the enantioselectivity of the reaction, but did not increase the rate of reaction. The enantioselectivity could be further increased by reducing the reaction temperature to −40 °C (Table 1: entry 5), and both the conversion and enantioselectivity could be restored to the previously reported values by use of 2 mol % of complex **1** in conjunction with 10 mol % of potassium cyanide (Table 1: compare entries 1 and 6). However, further reduction of the reaction temperature to −70 °C completely suppressed the formation of compound **13**, even when 5 mol % of catalyst **1** was used with 10 mol % of potassium cyanide (Table 1: entry 7).

Under the optimal conditions developed for the addition of ethyl cyanoformate to benzaldehyde (Table 1: entry 6), a range of other cyanoformates were found to add to aldehydes to form cyanohydrin carbonates. Thus, benzaldehyde and pivaldehyde were selected as representative aromatic and aliphatic aldehydes and the asymmetric addition of methyl cyanoformate,[27,29,40] benzyl cyanoformate[27,29] and *tert*-butyl cyanoformate[32,34] to these aldehydes was investigated (Scheme 5). The results of this study are shown in Table 2. The cyanohydrin benzyl carbonates **14b**,**e** and the *tert*-butyl carbonate **14c** were too non-volatile to analyse by chiral GC, though they were formed in quantitative yields (Table 2; entries 3,4 and 7). However, comparison of the enantiomeric excesses obtained for cyanohydrin carbonates **14a** and **13a** (Table 2: entries 1 and 2) and of cyanohydrin carbonates **13g**, **14d** and **14f** (Table 2: entries 5, 6 and 8) revealed that the structure of the cyanoformate did not have a significant influence on the enantioselectivity of the formation of cyanohydrin carbonates.



Scheme 5.

Having determined the optimal reaction conditions and that varying the structure of the cyanoformate was not beneficial, the asymmetric addition of ethyl cyanoformate to six other aldehydes was investigated. The results are shown in Table 3. Electron rich aromatic aldehydes (Table 3: entries 1 and 2) and cinnamaldehyde (Table 3: entry 4) are excellent

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

Entry	**1** (mol %)	KCN (mol %)	Temp (°C)	Time (h)	Completion (%)	ee[b] (%)
1[c]	5	0	−40	18	100	95 (*S*)
2	1	0	25	90	5	89 (*S*)
3	1	1	25	48	100	51 (*S*)
4	1	10	25	48	98	68 (*S*)
5	1	10	−40	19	87	81 (*S*)
6	2	10	−40	26	100	95 (*S*)
7	5	10	−70	24	0	

[a] Reactions were carried out in dichloromethane using 1.2 equiv of EtOCOCN unless otherwise stated.
[b] Enantiomeric excesses were determined by chiral GC.
[c] Result taken from Ref. 24 and using 2 equiv of ethyl cyanoformate.

Table 2. The asymmetric addition of cyanoformates to aldehydes catalysed by complex **1** and potassium cyanide[a]

Entry	Substrate	Product	Cyanoformate	Yield (%)	ee[b] (%)
1	PhCHO	**14a**	MeOCOCN	92	95
2	PhCHO	**13a**	EtOCOCN	100	95
3	PhCHO	**14b**	BnOCOCN	100	[c]
4	PhCHO	**14c**	^{t}BuOCOCN	100	[c]
5	^{t}BuCHO	**14d**	MeOCOCN	85	62
6	^{t}BuCHO	**13g**	EtOCOCN	79	68
7	^{t}BuCHO	**14e**	BnOCOCN	100	[c]
8	^{t}BuCHO	**14f**	^{t}BuOCOCN	100	65

[a] Reactions were conducted at −40 °C for 24 h in dichloromethane using 1.2 equiv of the cyanoformate with complex **1** (2 mol %) and KCN (10 mol %) as catalysts.
[b] Enantiomeric excesses were determined by chiral GC.
[c] Could not be determined, but the product was optically active.

Table 3. The asymmetric addition of ethyl cyanoformate to aldehydes catalysed by complex **1** and potassium cyanide[a]

Entry	Substrate	**1** (mol %)	Product	Yield (%)	ee[b] (%)
1	PhCHO	2	**13a**	100	95 (95)
2	4-MeOC$_6$H$_4$CHO	2	**13b**	98	97 (95)
3	4-(CF$_3$)C$_6$H$_4$CHO	1	**13c**	100	69 (76)
4	PhCH=CHCHO	2	**13d**	94	95 (94)
5	CH$_3$(CH$_2$)$_7$CHO	2	**13e**	90	79 (84)
6	CyCHO	1	**13f**	86	74 (79)
7	^{t}BuCHO	2	**13g**	79	68 (76)

[a] Reactions were conducted at −40 °C for 24 h in dichloromethane using 1.2 equiv of EtOCOCN with complex **1** (2 mol %) and KCN (10 mol %) as catalysts.
[b] Enantiomeric excesses were determined by chiral GC. The value in brackets is that reported in Ref. 24 for the use of catalyst **1** (5 mol %) in the absence of KCN. In each case, the (*S*)-enantiomer of the cyanohydrin carbonate was formed from (*R*,*R*)-**1**.

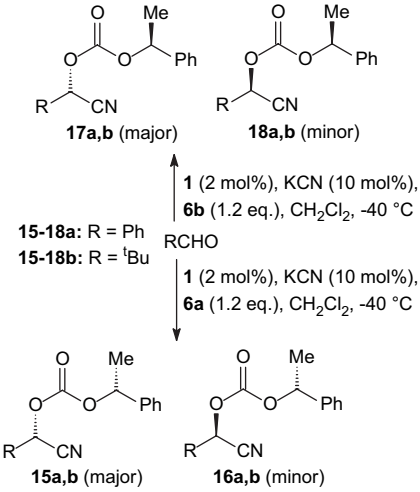
substrates for the reaction under these conditions, giving cyanohydrin ethyl carbonates **13a**,**b**,**d** in high yields and with high enantiomeric excesses. In contrast, *para*-trifluoromethylbenzaldehyde gave cyanohydrin ethyl carbonate **13c** with much lower enantiomeric purity, though still in high yield (Table 3: entry 3). The apparently lower asymmetric induction obtained using this substrate may be due to its inherently high reactivity (as a result of which only 1 mol % of catalyst **1** was required to obtain quantitative conversion into product **13c**) towards nucleophilic addition enhancing the rate of the racemic background reaction. However, product **13c** was also found to racemise on standing, so it may be that the enantiomeric excess of the product is not truly representative of the asymmetric induction in this case.

All the three aliphatic aldehydes studied gave products with lower enantiomeric excesses than the electron rich aromatic aldehydes, as is generally observed for the asymmetric synthesis of cyanohydrin derivatives. However, the reaction appears to be sensitive to the steric environment of the aldehyde as both the chemical yield and the enantiomeric excess of the product decreased as the carbonyl became more sterically hindered (Table 3: entries 5–7). Attempts were also made to use ketones as substrates, but no reaction occurred with either acetophenone or heptan-2-one, even when 5 mol % of catalyst **1** was used along with 10 mol % of potassium cyanide at room temperature.

2.3. Cyanide ion cocatalysis in the diastereoselective synthesis of cyanohydrin carbonates from chiral cyanoformates

Previous studies on the asymmetric synthesis of cyanohydrin carbonates have always employed simple achiral cyanoformates, usually the methyl[22,27,29] or ethyl[18,19,24,28,29] derivatives. However, in view of the compatibility of the catalyst **1**/potassium cyanide system with a wide range of cyanoformates (Table 2), we felt that it was worthwhile investigating the use of more complex cyanoformates, and in particular those which are themselves chiral so as to achieve a diastereomeric cyanohydrin synthesis. This was particularly attractive as there were no previous reports on the synthesis of cyanohydrin derivatives using chiral cyanide sources.

For the initial studies, (*R*)- and (*S*)-1-phenylethyl cyanoformates **6a**,**b** were selected as the chiral cyanoformates since both enantiomers of the precursor alcohol **7a**,**b** are available and this would allow any matched/mismatched pairs with (*R*,*R*)-catalyst **1** to be identified. Benzaldehyde and pivaldehyde were again selected as representative aromatic and aliphatic aldehydes. Control experiments confirmed that even at room temperature, neither potassium cyanide (2 mol %) nor complex **1** (2 mol %) alone would induce any reaction between cyanoformates **6a**,**b** and benzaldehyde. However, under the optimal conditions developed for use of ethyl cyanoformate (Table 1: entry 6), cyanoformates **6a**,**b** did react with both benzaldehyde and pivaldehyde to give a mixture of cyanohydrin carbonates **15a**,**b**, **16a**,**b** and **17a**,**b**, **18a**,**b**, respectively, as shown in Scheme 6 and detailed in Table 4. Reactions involving benzaldehyde as substrate did not go to completion even after the addition of a second batch of catalyst **1** and potassium cyanide and at a total reaction time of 72 h. In contrast, pivaldehyde was found to be converted quantitatively into products **15**–**18b** after a reaction time of 24 h.



Scheme 6.

Table 4. Diastereoselective synthesis of cyanohydrin carbonates derived from chiral cyanoformates **6a**,**b**

Entry	Aldehyde	Cyanoformate (major product)	Conversion (%)	Diastereomeric ratio[c]
1[a,b]	PhCHO	**6a** (**15a**)	88	28:1 (93% de)
2[a,b]	PhCHO	**6b** (**17a**)	66	18:1 (89% de)
3[a]	^{t}BuCHO	**6a** (**15b**)	100	5.3:1 (68% de)
4[a]	^{t}BuCHO	**6b** (**17b**)	100	3.6:1 (57% de)

[a] Reactions were conducted at −40 °C for 24 h in dichloromethane using 1.2 equiv of cyanoformate **6a** or **6b** with complex **1** (2 mol %) and KCN (4 mol %) as catalysts.
[b] After 24 h, additional complex **1** (2 mol %) and KCN (4 mol %) were added and the reaction mixture was stirred for a further 48 h at −40 °C.
[c] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

In each case, the NMR spectra of the product mixture indicated that the major product obtained using cyanoformate **6a** was enantiomeric with the minor product obtained using cyanoformate **6b**. This indicated that it was the stereochemistry of catalyst **1** rather than that of the cyanoformates **6a**,**b** was the dominant factor in determining the stereochemistry of compounds **15**–**18**. On this basis, the stereochemistry of the products was expected to be as shown in Scheme 6, since in every case studied to date the (*R*,*R*)-enantiomer of catalyst **1** induces the addition of a cyanide source to the *re*-face of an aldehyde to give a cyanohydrin derivative with (*S*)-configuration (except in few cases where the Cahn–Ingold–Prelog priority rules result in the cyanohydrin derivative having (*R*)-configuration). This stereochemical assignment was confirmed by crystal structures (Figs. 1 and 2) of the major diastereomer obtained from the reaction between benzaldehyde or pivaldehyde and cyanoformate **6a**, which showed that in each case the two stereocentres had opposite configurations and hence confirmed the assignment of structures **15a**,**b** to these compounds. The very small crystals of **15a** were twinned and gave weak diffraction data, limiting the precision of the derived structure, but the relative stereochemistry is unambiguous. There are two molecules in the

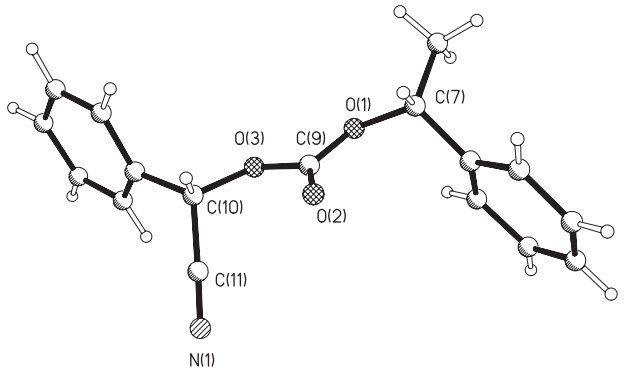


Figure 1. The structure of one of the two independent molecules of cyanohydrin carbonate **15a**; the other molecule is almost identical.

asymmetric unit. For these and the unique molecule of **15b**, geometrical parameters are unexceptional. There are no significant direction-specific intermolecular interactions in either of the crystal structures. Full details are given in the supplementary material.

It is apparent from Table 4 that the combination of (*R*,*R*)-**1** with cyanoformate **6a** constitutes a matched pair, whilst the combination of (*R*,*R*)-**1** and **6b** forms a mismatched pair (compare Table 4: entries 1,2 and 3,4). Notably, the diastereomeric excesses obtained for the matched pair were comparable with the enantiomeric excesses obtained when the same aldehyde was reacted with ethyl cyanoformate (compare Table 3: entry 1 with Table 4: entry 1 and Table 3: entry 7 with Table 4: entry 3).

The reaction of cyanoformates **10a–d** with benzaldehyde and pivaldehyde in the presence of complex **1** and potassium cyanide was also investigated. However, only in the case of lactate derived cyanoformate **10a** did any reaction occur under the conditions shown in Scheme 6, and in this case the conversions (28–54%) were significantly lower than those observed using cyanoformates **6a**,**b**. Cyanoformates **10b–d** also failed to react when the reactions were left for 2 weeks at room temperature.

Since only one enantiomer of cyanoformate **10a** had been prepared, reactions were carried out using both enantiomers of catalyst **1** and either benzaldehyde or pivaldehyde as substrate to give cyanoformates **19a**,**b** and **20a**,**b**, respectively,

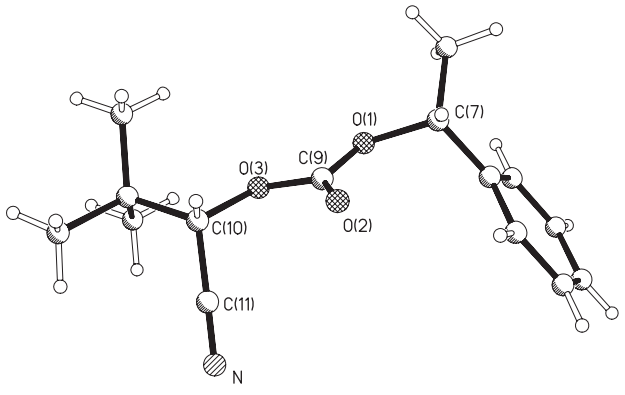
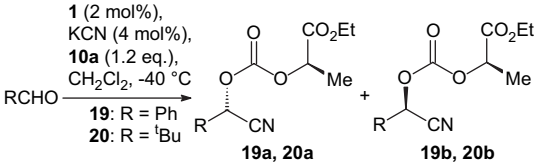


Figure 2. The molecular structure of cyanohydrin carbonate **15b**.

as shown in Scheme 7. The results of this study are shown in Table 5. In each case, ^{1}H NMR analysis of the product mixture showed that the major product obtained using catalyst (*R*,*R*)-**1** was diastereomeric with the major product obtained using catalyst (*S*,*S*)-**1**, consistent with predominant catalyst control of the stereochemistry as observed using cyanoformates **6a**,**b**. In this case, the reactions did not show a significant double asymmetric induction effect, and when pivaldehyde was used as substrate, the use of the (*S*,*S*)-enantiomer of catalyst **1** actually gave a slightly higher diastereoselectivity than the use of the (*R*,*R*)-enantiomer of the catalyst (Table 5: entries 3 and 4).



Scheme 7.

Table 5. Diastereoselective synthesis of cyanohydrin carbonates derived from chiral cyanoformate **10a**[a]

Entry	Aldehyde	Catalyst	Conversion (%)	Diastereomeric ratio[b]
1	PhCHO	(*R*,*R*)-**1**	32	**19a/19b**=12.3:1 (85% de)
2	PhCHO	(*S*,*S*)-**1**	54	**19b/19a**=9:1 (80% de)
3	^{t}BuCHO	(*R*,*R*)-**1**	28	**20a/20b**=10.8:1 (83% de)
4	^{t}BuCHO	(*S*,*S*)-**1**	46	**20b/20a**=13.3:1 (86% de)

[a] Reactions were conducted at −40 °C for 24 h in dichloromethane using 1.2 equiv of cyanoformate **10a** with complex **1** (2 mol %) and KCN (4 mol %) as catalysts.
[b] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

2.4. A homogeneous system for the asymmetric synthesis of cyanohydrin carbonates

Whilst the addition of solid potassium cyanide to reactions between aldehydes and cyanoformates did allow the amount of chiral catalyst used to be reduced to just 1–2 mol %, the heterogeneous nature of these reactions was a concern, especially for larger scale reactions and also meant that the reaction kinetics could not be analysed. The complex formed between potassium cyanide and 18-crown-6 is known to be soluble in dichloromethane,[41] so the use of this complex to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes under homogeneous reaction conditions was investigated.[42]

When benzaldehyde was used as the substrate, it was found that the potassium cyanide/18-crown-6 complex would indeed cocatalyse the synthesis of mandelonitrile ethyl carbonate at −40 °C, and that the amount of catalyst **1** required could be further reduced to 1.5 mol %. However, the amount of the potassium cyanide/18-crown-6 complex used was found to be critical. Use of 3 mol % of potassium cyanide/18-crown-6 complex gave mandelonitrile ethyl carbonate with just 17% enantiomeric excess presumably due to a facile uncatalysed addition of cyanide to the aldehyde in the presence of high concentrations of soluble cyanide. In contrast, use of less than 1 mol % of potassium

cyanide/18-crown-6 complex was ineffective as no reaction occurred. Thus, the use of 1 mol % of potassium cyanide/18-crown-6 complex and 1.5 mol % of catalyst **1** was adopted as the standard conditions, and under these conditions benzaldehyde was completely converted into (*S*)-mandelonitrile ethyl carbonate with 91% enantiomeric excess. Under these conditions, the reaction between a range of aldehydes and ethyl cyanoformate was studied and the results are presented in Table 6.

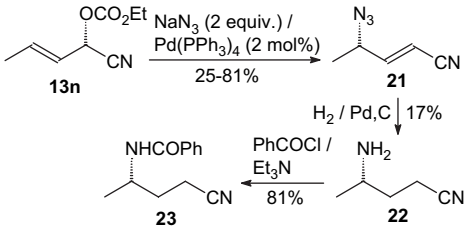
Table 6. Potassium cyanide/18-crown-6 induced synthesis of cyanohydrin ethyl carbonates[a]

Entry	Aldehyde	Product	Conversion (%)	ee[c] (%)
1	PhCHO	**13a**	100	91 (*S*)
2	2-MeC_6H_4CHO	**13h**	100	97 (*S*)
3	4-MeC_6H_4CHO	**13i**	100	99 (*S*)
4	2-$MeOC_6H_4CHO$	**13j**	100	100 (*S*)
5	3-$MeOC_6H_4CHO$	**13k**	100	97 (*S*)
6	4-$MeOC_6H_4CHO$	**13b**	100	90 (*S*)
7	2-ClC_6H_4CHO	**13l**	100	93 (*S*)
8	4-ClC_6H_4CHO	**13m**	100	100 (*S*)
9	PhCH=CHCHO	**13d**	100[b]	90 (*S*)
10	MeCH=CHCHO	**13n**	100	93 (*S*)
11	EtCH=CHCHO	**13o**	100	91 (*S*)
12	MeCH=C(Me)CHO	**13p**	100[b]	89 (*S*)
13	$CH_3(CH_2)_7CHO$	**13e**	98	81 (*S*)
14	CyCHO	**13f**	100	78 (*S*)
15	Me_3CCHO	**13g**	100	71 (*S*)

[a] Reactions were conducted at −40 °C for 24 h (unless stated otherwise) in dichloromethane using 1.2 equiv of ethyl cyanoformate with complex **1** (1.5 mol %) and KCN/18-crown-6 (1 mol %) as catalysts.
[b] Reaction required 48 h to go to completion.
[c] ee values were determined by chiral GC and are accurate to ±4%.

The enantioselectivities reported in Table 6 are comparable to those obtained in the absence of cyanide,[24] and to those obtained using potassium cyanide under heterogeneous conditions (Table 3). In every case, the (*S*)-cyanohydrin carbonate was obtained from the (*R*,*R*)-enantiomer of catalyst **1**. Thus, electron rich aromatic aldehydes (Table 6: entries 1–6) were found to be excellent substrates as were chlorinated benzaldehydes (Table 6: entries 7 and 8). In the case of the products derived from 2-methoxybenzaldehyde and 4-chlorobenzaldehyde, only one enantiomer could be detected by chiral GC. Four α,β-unsaturated aldehydes were investigated as the β,γ-unsaturated cyanohydrin carbonates derived from these substrates are known to be substrates for palladium catalysed allylic substitution chemistry,[22,43] thus enhancing the range of chiral products available from chiral cyanohydrins. In each case, the α,β-unsaturated aldehydes gave a cyanohydrin ethyl carbonate with around 90% enantiomeric excess (Table 6: entries 9–12), though two of these reactions (Table 6: entries 9 and 12) were slow, requiring 48 h to go to completion. Finally, three representative aliphatic aldehydes were investigated (Table 6: entries 13–15) and gave products with 71–81% enantiomeric excess, which in each case is comparable to the enantioselectivity obtained in the absence of any cyanide and to that obtained in the presence of solid potassium cyanide (Table 3: entries 5–7). Hence, the combination of complex **1** (1.5 mol %) and the potassium cyanide/18-crown-6 complex (1 mol %) constitutes a highly effective catalytic system for the asymmetric synthesis of a variety of cyanohydrin carbonates.

To illustrate the utility of β,γ-unsaturated cyanohydrin carbonates, compound **13n** was treated with sodium azide in the presence of tetrakis(triphenylphosphine)palladium(0) under conditions previously reported by Deardorff et al.[43b] to give γ-azido-α,β-unsatured nitrile **21** as shown in Scheme 8. Compound **21** was formed as a 4:1 ratio of *E*- and *Z*-isomer.[43b] Subsequent hydrogenation of compound **21** resulted in the formation of γ-amino nitrile **22**, which was converted into *N*-benzoyl derivative **23** for characterisation. Chiral GC analysis showed that compound **23** had an enantiomeric excess of 80%, a result, which is consistent with the findings of Deardorff et al. on the partial racemisation of cyanohydrin derivatives during palladium catalysed allylic substitution.[43a]



Scheme 8.

2.5. Reaction kinetics for the asymmetric addition of ethyl cyanoformate to benzaldehyde in the presence of potassium cyanide/18-crown-6

To obtain a better understanding of the processes occurring during the potassium cyanide/18-crown-6 complex catalysed processes, the reaction kinetics were monitored. These reactions were conducted at 22 °C using benzaldehyde as substrate, and at appropriate intervals samples were withdrawn and analysed by ^{1}H NMR spectroscopy to determine the ratio of benzaldehyde to mandelonitrile ethyl carbonate. Under these conditions, no side reactions occurred to interfere with the kinetic data.

Figure 3 shows the first order kinetic plots for reactions carried out in the absence of any potassium cyanide/18-crown-6 complex (using 5 mol % of catalyst **1**) and in the presence of increasing amounts of the potassium cyanide/18-crown-6 complex (using 2 mol % of catalyst **1**). Reactions carried out with no potassium cyanide/18-crown-6 complex or with 0.5–1.0 mol % of the potassium cyanide/18-crown-6 complex are clearly not first order (and also do not fit second or third order), whilst reactions carried out in the presence of 2–4 mol % of the potassium cyanide/18-crown-6 complex show an increasingly good fit to first order kinetics, as expected based on the previous work using trimethylsilyl cyanide as the cyanide source.[5b,6]

We have previously proposed a mechanism for the asymmetric synthesis of cyanohydrin carbonates using catalyst **1**, in which complex **1** is proposed to react with the cyanoformate to form species **24** (Scheme 9).[18] Complex **24** then decomposes to bis-cyanide complex **25**, which is a key intermediate needed to start the catalytic cycle. The kinetic results presented above suggest that in the absence of potassium cyanide/18-crown-6, the conversion of complex **24** into bis-cyanide **25** occurs at a rate, which is comparable to or

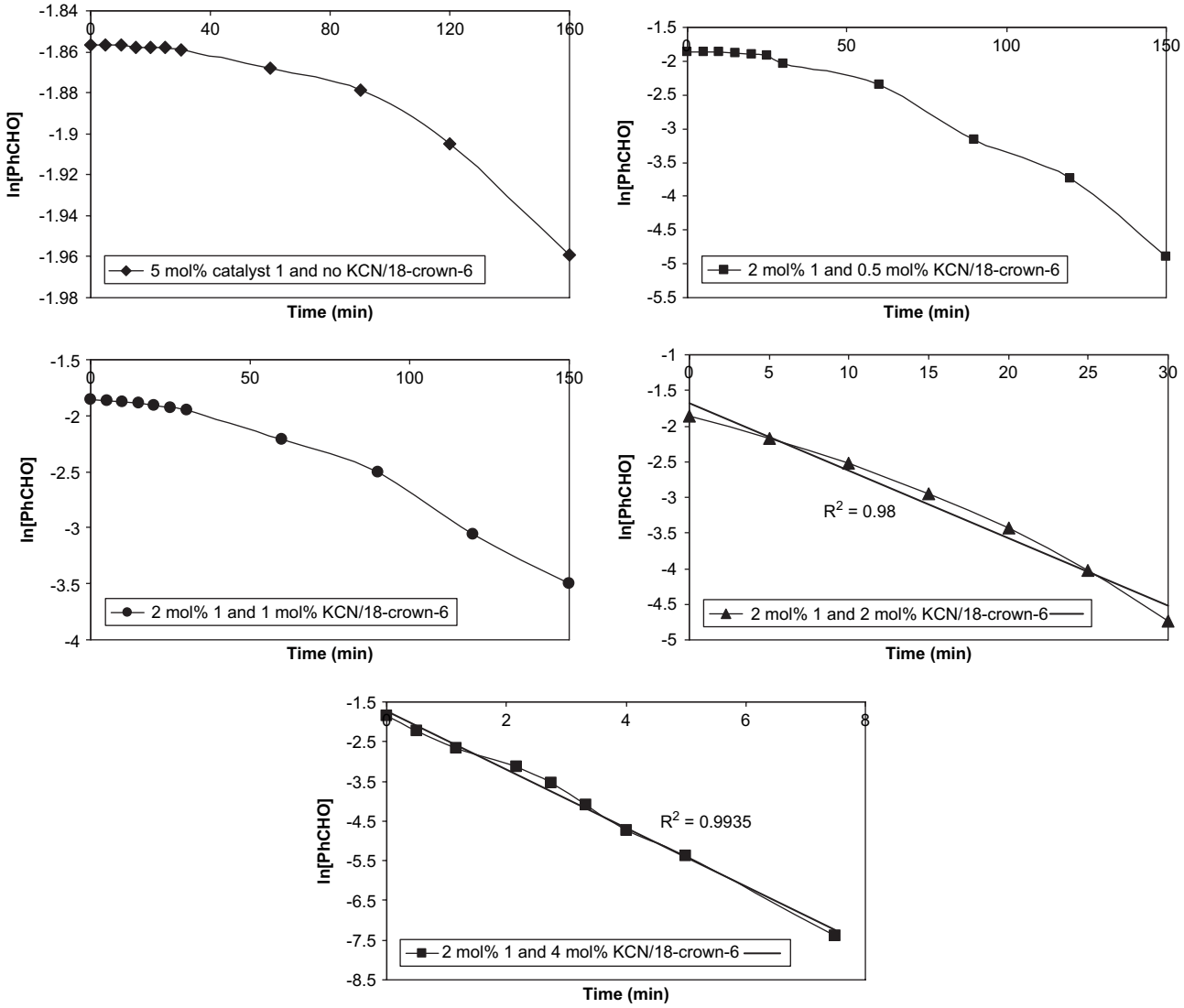


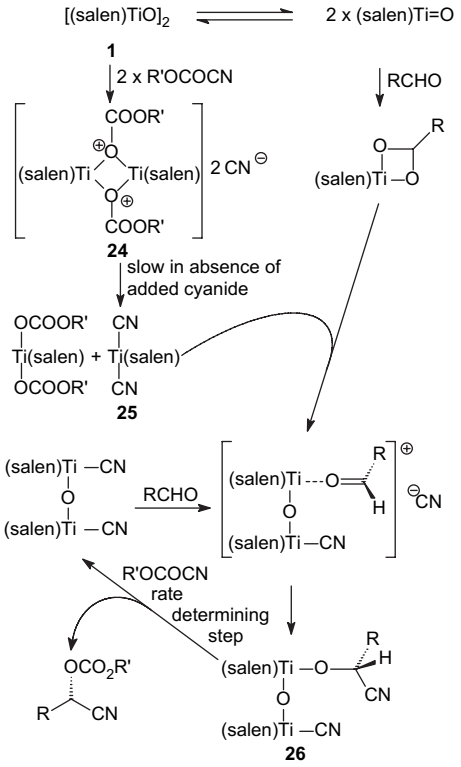
Figure 3. First order kinetic plots for the addition of ethyl cyanoformate to benzaldehyde in the presence of varying amounts of the potassium cyanide/18-crown-6 complex.

slower than the release of the titanium bound cyanohydrin **26**, which is the rate determining step when trimethylsilyl cyanide is used as the cyanating agent.[5b,6] Increasing the concentration of cyanide ions would then increase the rate at which **24** was converted into **25**, resulting in the release of titanium bound cyanohydrin **26** again becoming the rate determining step in the catalytic cycle, and thus restoring the overall first order kinetics.

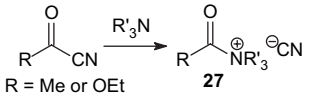
2.6. Relationship to other work on the asymmetric addition of ethyl cyanoformate to aldehydes using titanium(salen) complexes

Moberg has reported that the asymmetric addition of ethyl cyanoformate (or acetyl cyanide) to aldehydes catalysed by complex **1** is accelerated in the presence of a tertiary amine.[19] In view of the results we have obtained on cyanide catalysis, Moberg's results could be explained by the reaction of tertiary amine with the ethyl cyanoformate (or acetyl cyanide) to generate cyanide ions (Scheme 10). These then catalyse the formation of complex **26** as shown in Scheme 9. Complex **26** can then react either with ethyl cyanoformate (which will regenerate the cyanide catalyst directly) or with the more reactive ammonium salt **27** (which regenerates the tertiary amine, which can then react with another molecule of the ethyl cyanoformate or acetyl cyanide to regenerate the cyanide cocatalyst) to form the cyanohydrin ethyl carbonate (or acetate) product.

However, Moberg recently reported[19c] that when $H^{13}CN$ was added to the reaction mixture, no ^{13}C incorporation into the cyanohydrin occurred. This appeared to rule out the presence of cyanide ions in the reaction mixture, and on this basis Moberg proposed the alternative transition state shown in Figure 4. Whilst the transition state structure shown in Figure 4 appears to neatly explain Moberg's findings, it suffers from two difficulties. Firstly, it is not easily extendable to cyanide sources such as trimethylsilyl cyanide, which does not contain a carbonyl bond. Since trimethylsilyl cyanide is known to be an excellent substrate[5,6] for catalyst **1**, this is a major limitation. Secondly, both the titanium ions in the structure given in Figure 4 are in the +3 oxidation state



Scheme 9.



Scheme 10.

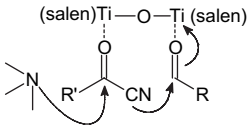


Figure 4. Moberg's mechanism for addition of acyl cyanides to aldehydes in the presence of triethylamine.[19c]

and there is no precedent for the formation of Ti(III)(salen) complexes, and no indication was given on how complex **1** could be reduced under the reaction conditions. Monitoring of our reactions involving complex **1** by ^{1}H NMR spectroscopy gave no evidence for the formation of paramagnetic species in situ. Thus, the transition state shown in Figure 4 appears non-viable, and the mechanistic explanation given in Scheme 9 and involving species **27** is more likely. The lack of ^{13}C incorporation may be due to slow exchange between the titanium associated cyanide counterions (which will come exclusively from acetyl cyanide) and free hydrogen cyanide present in the solution.

Feng has recently reported the asymmetric addition of ethyl cyanoformate to aldehydes catalysed by a titanium complex generated in situ from a salen ligand (optimally the same ligand used for the synthesis of complexes **1** and **2**) and titanium tetra-isopropoxide.[26] It was found that the reactions were accelerated by the presence of excess isopropanol, and Feng interpreted this on the basis of catalysis by a monomeric titanium complex, which is only formed in the presence of excess isopropanol to inhibit the formation of bimetallic complex **1**. However, we have previously shown that monomeric titanium(salen) complexes are catalytically inactive in asymmetric cyanohydrin synthesis and demonstrated that any catalysis observed is due to adventitious moisture in the reactions resulting in the formation of catalytically active bimetallic complex **1**.[5] An alternative explanation of Feng's results, therefore, is that the isopropoxide reacts with ethyl cyanoformate to form isopropyl ethyl carbonate and cyanide. The latter then catalyses the asymmetric addition of ethyl cyanoformate to the aldehyde as shown in Scheme 9.

3. Conclusions

By studying the reaction kinetics, it has been shown that cyanide ion acts as a cocatalyst in the asymmetric synthesis of cyanohydrin carbonates catalysed by Ti(salen) complex **1**. This knowledge has allowed the development of reaction conditions under which the amount of catalyst **1** required to accomplish this transformation can be reduced to just 1.5–2 mol % by use of either solid potassium cyanide or the potassium cyanide/18-crown-6 complex as cocatalysts. Under these optimised conditions, both achiral and chiral cyanoformates were found to undergo enantio- and diastereoselective additions to a range of aldehydes to form highly enantio- and diastereomerically enriched cyanoformates. The stereochemistry of the major diastereomer of the cyanohydrin carbonate formed from (*R*)-1-phenylethyl cyanoformate **6a** and both benzaldehyde and pivaldehyde was unambiguously determined by X-ray crystallography and the results indicate that the stereochemistry of catalyst **1** rather than that of the cyanoformate is the dominant factor in determining the stereochemistry of the cyanoformate derivatives.

The reaction kinetics indicate that provided at least 2 mol % of the potassium cyanide/18-crown-6 complex is employed, the reactions display first order kinetics consistent with the mechanistic cycle previously proposed for related reactions employing trimethylsilyl cyanide as the cyanide source. This mechanistic cycle and cyanide ion catalysis also provide a single, unified explanation of previous results on the asymmetric addition of ethyl cyanoformate to aldehydes catalysed by titanium(salen) complexes in the presence of tertiary amines or alcohols as cocatalysts.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 or 360 spectrometer (^{1}H 300/360 MHz, ^{13}C 75/90 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 FTIR Paragon 1000 spectrometer, as a thin film between NaCl plates or on the pure solid using ATR. 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 AX505 W spectrometer within the Chemistry Department at King's College. The sample was ionised by electron ionisation (EI), chemical ionisation (CI), fast atom bombardment (FAB) or electrospray ionisation (ESI). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter or a Polaar 2001 Optical Activity automatic 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). Melting points are uncorrected and were recorded on a Barnstead Electrothermal 9100 melting point apparatus.

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 F_{254}, 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.

4.2. Synthesis of chiral cyanoformates

4.2.1. Ethyl (*R*)-1-phenylethyl oxalate 8a. A stirred solution of (*R*)-1-phenylethanol **7a** (6.9 g, 56.5 mmol) and pyridine (4.5 g, 57.0 mmol) in CH_2Cl_2 (24 mL) was cooled in an ice bath and ethyl oxalyl chloride (7.8 g, 57.0 mmol) was added over 1 h. The mixture was stirred in an ice bath for 4 h, then at room temperature overnight. The reaction mixture was washed with water (2×6 mL), dried ($MgSO_4$) and solvent evaporated in vacuo to leave diester **8a** (12.2 g, 97%) as a colourless liquid. $[\alpha]_D^{20}$ +60.0 (*c* 1.25, $CHCl_3$); ν_{max} (neat) 2985 s and 1740 s cm^{-1}; δ_H ($CDCl_3$) 1.38 (3H, t, *J* 7.1 Hz, CH_3), 1.68 (3H, d, *J* 6.6 Hz, CH_3), 4.35 (2H, q, *J* 7.1 Hz, CH_2), 6.03 (1H, q, *J* 6.6 Hz, CH), 7.3–7.4 (5H, m, ArH); δ_C ($CDCl_3$) 158.3 (C═O), 157.7 (C═O), 140.4 (ArC), 128.9 (ArCH), 128.8 (ArCH), 126.6 (ArCH), 75.9 (OCH), 63.4 (OCH_2), 22.2 (CH_3), 14.2 (CH_3); *m/z* (CI) 223 (MH^+, 24), 209 (52), 131 (35), 106 (67), 105 (100), 104 (46), 77 (48), 51 (15). Found (ESI) 245.0783; $C_{12}H_{14}O_4Na$ $(M+Na)^+$ requires 245.0784.

4.2.2. Ethyl (*S*)-1-phenylethyl oxalate 8b. Prepared from (*S*)-1-phenylethanol **7b** (5.0 g, 40.9 mmol) as described for the (*R*)-enantiomer **8a** (Section 4.2.1) to give compound **8b** (9.0 g, 97%) as a colourless liquid. $[\alpha]_D^{20}$ −60.0 (*c* 1.1, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer **8a**.

4.2.3. (*R*)-1-Phenylethyl oxamide 9a from diester 8a. To a solution of compound **8a** (17.3 g, 78.2 mmol) in ethanol (9 mL) was added 0.88 ammonia (5.4 mL) in 4–5 portions with swirling over 3–5 min. The solution was allowed to stand at room temperature for 3 days and then diluted with CH_2Cl_2 (34 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to leave an oil, which solidified on standing. The solid was washed with 40–60 petroleum ether, recrystallised from toluene (50 mL) and washed again with 40–60 petroleum ether. Further recrystallisation from toluene/methanol (9:1) gave compound **9a** (3.0 g, 20%) as white crystals. Mp 89.5–90.5 °C (from benzene/60–90 petroleum ether); $[\alpha]_D^{20}$ +109.1 (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3403 s, 3234 s, 1736 s and 1688 s cm^{-1}; δ_H ($CDCl_3$) 1.68 (3H, d, *J* 6.6 Hz, CH_3), 5.99 (1H, q, *J* 6.6 Hz, CH), 6.61 (1H, br, NH), 6.98 (1H, br, NH), 7.3–7.4 (5H, m, ArH); δ_C ($CDCl_3$) 159.9 (C═O), 159.1 (C═O), 140.4 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.7 (ArCH), 76.4 (OCH), 22.3 (CH_3); *m/z* (CI) 211 ($M+NH_4^+$, 100). Found (ESI) 216.0628; $C_{10}H_{11}NO_3Na$ $(M+Na)^+$ requires 216.0631.

4.2.4. (*S*)-1-Phenylethyl oxamide 9b from diester 8b. Prepared from compound **8b** (9.0 g, 40.7 mmol) as described for the (*R*)-enantiomer **9a** (Section 4.2.3) to give compound **9b** (2.9 g, 37%) as white crystals. $[\alpha]_D^{20}$ −109.3 (*c* 0.45, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer **9a**.

4.2.5. (*S*)-1-Phenylethyl oxamide 9b from alcohol 7b. A solution of (*S*)-phenylethanol **7b** (1.0 g, 8.2 mmol) in CH_2Cl_2 (10 mL) was stirred and cooled in an ice bath. Oxalyl chloride (2.1 g, 16.4 mmol) was added dropwise and the resulting mixture was stirred for 1 h at room temperature. The solvent and excess oxalyl chloride were removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C in an ice bath. A saturated solution of ammonia in THF (0.2 mL, excess) was added dropwise, and the resulting mixture was stirred for 15 min. The reaction mixture was washed with water (40 mL), the aqueous layer was extracted with CH_2Cl_2 (40 mL) and the combined organic layers were washed with water (40 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was recrystallised from a toluene/hexane mixture to give oxamide **9b** (0.90 g, 98%) as a white solid.

4.2.6. (*R*)-1-Phenylethyl cyanoformate 6a. To a stirred mixture of oxamide **9a** (2.9 g, 15.0 mmol) and pyridine (4.6 g, 57.8 mmol) in CH_2Cl_2 (27 mL), in an ice bath, TFAA (3.8 g, 17.9 mmol) was added dropwise over 10 min. The ice bath was removed and the thick reaction mixture was allowed to stir at room temperature for 2 h. Water (58 mL) was added, the organic layer was separated, washed with water (43 mL) and the aqueous layer extracted with CH_2Cl_2 (2×30 mL). The combined CH_2Cl_2 layers were again washed with water (50 mL), dried ($MgSO_4$) and evaporated in vacuo to leave an oil, which was subjected to bulb-to-bulb distillation (120–170 °C at 150 mmHg) to give compound **6a** (1.9 g, 71%) as a colourless oil. $[\alpha]_D^{20}$ +95.6 (*c* 1.65, $CHCl_3$); ν_{max} (neat) 2244 s and 1744 s cm^{-1}; δ_H ($CDCl_3$) 1.71 (3H, d, *J* 6.5 Hz, CH_3), 6.06 (1H, q, *J* 6.5 Hz, CH), 7.3–7.4 (5H, m, ArH); δ_C ($CDCl_3$) 144.0 (C═O), 138.8 (ArC), 129.6 (ArCH), 129.3 (ArCH), 126.8 (ArCH), 109.8 (CN), 78.8 (OCH), 21.9 (CH_3); *m/z* (EI)

175 (M^+, 38), 159 (12), 132 (11), 121 (11), 105 (100), 77 (24). Found (ESI) 293.1147; $C_{17}H_{18}O_3Na$ ($2M-CO(CN)_2+Na)^+$ requires 293.1148. Compound reacts with water under electrospray mass spectrometric conditions to form $(PhCHMeO)_2CO$ in situ.

4.2.7. (*S*)-1-Phenylethyl cyanoformate 6b. Prepared from compound **9b** (1.1 g, 5.7 mmol) as described for the (*R*)-enantiomer **6a** (Section 4.2.6) to give compound **6b** (0.85 g, 85%) as a colourless oil. $[\alpha]_D^{20}$ −95.6 (*c* 1.35, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer **6a**.

4.2.8. (*R*)-1-(Carboxyethyl)ethyl oxamide 12a. To a stirred solution of ethyl lactate (1.0 g, 7.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C, oxalyl chloride (2.0 g, 15.4 mmol) was added dropwise. The ice bath was removed and the mixture was stirred for 1 h, after which the solvent was removed in vacuo and the residue dried on a vacuum line. The resulting crude mono-ester was redissolved in CH_2Cl_2, cooled to 0 °C and concentrated aqueous ammonia (0.46 mL, 1.2 equiv) was added. The mixture was stirred for 30 min, then water was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was recrystallised from CH_2Cl_2 to give oxamide **12a** (0.44 g, 27%) as a white solid. Mp 77–79 °C; $[\alpha]_D^{20}$ −36.5 (*c* 0.26, $CHCl_3$); ν_{max} (CH_2Cl_2) 3349 w, 3239 w, 3222 w, 1733 s, 1676 s and 1667 s cm^{-1}; δ_H ($CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz, CH_3CH_2), 1.61 (3H, d, *J* 7.0 Hz, CH_3CH), 4.21 (2H, q, *J* 7.1 Hz, OCH_2), 5.18 (1H, q, *J* 7.0 Hz, CH_3CHO), 6.00 (1H, br, NH_2), 6.92 (1H, br, NH_2); δ_C ($CDCl_3$) 169.5 (C=O), 159.6 (C=O), 157.8 (C=O), 71.5 (OCH), 62.1 (OCH_2), 17.0 (CH_3), 14.3 (CH_3); *m/z* (ESI) 207 ($M+NH_4^+$, 80%), 180 (100). Found (ESI) 207.0978; $C_7H_{15}N_2O_5$ ($M+NH_4^+$) requires 207.0975.

4.2.9. (*R*)-1-(Carboxyethyl)benzyl oxamide 12b. Sodium hydride (22 mg of a 60% dispersion in mineral oil) was washed with petrol, suspended in THF (20 mL) and cooled in an ice bath. Ethyl mandelate (0.10 g, 0.56 mmol) was added, followed by dropwise addition of oxalyl chloride (0.14 g, 1.12 mmol). The ice bath was removed and the mixture was stirred for 16 h. The solvent was removed in vacuo, and the residue was dried on a vacuum line. The crude mono-ester was redissolved in CH_2Cl_2, and concentrated aqueous ammonia (0.20 mL, excess) was added at 0 °C. The mixture was stirred for 30 min, then water was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were washed with water (20 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give compound **12b** (0.15 g, 97%) as a white solid. Mp 190–200 °C (decomp.); $[\alpha]_D^{20}$ +4.7 (*c* 0.3, $CHCl_3$); ν_{max} (ATR) 3445 br, 2983 m, 1748 s and 1601 m cm^{-1}; δ_H ($CDCl_3$) 1.12 (3H, t, *J* 7.1 Hz, CH_3CH_2), 4.0–4.3 (2H, m, OCH_2CH_3), 5.91 (1H, s, PhCHO), 6.5–6.6 (1H, br, NH), 7.0–7.1 (1H, br, NH), 7.2–7.5 (5H, m, ArCH); δ_C ($CDCl_3$) 167.8 (C=O), 159.6 (C=O), 157.7 (C=O), 133.2 (ArC), 129.9 (ArCH), 129.2 (ArCH), 128.1 (ArCH), 73.4 (OCH), 62.4 (OCH_2), 14.2 (CH_3); *m/z* (CI) 269 ($M+NH_4^+$, 30%), 198 (70), 182 (100). Found (ESI) 269.1130; $C_{12}H_{17}N_2O_5$ ($M+NH_4^+$) requires 269.1132.

4.2.10. (+)-Menthyl oxamide 12c. To a stirred solution of (+)-menthol (1.0 g, 7.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C, oxalyl chloride (1.95 g, 15.4 mmol) was added dropwise. The ice bath was removed and the mixture was stirred for 1 h at room temperature. The solvent was then removed in vacuo, and the residue was dried on a vacuum line. The crude oxalic ester was redissolved in CH_2Cl_2 (50 mL), and concentrated aqueous ammonia (0.46 mL excess) was added at 0 °C. The mixture was stirred for 30 min, then water was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was recrystallised from CH_2Cl_2 to give compound **12c** (1.7 g, 97%) as a white solid. Mp 148–148.5 °C; $[\alpha]_D^{20}$ +87.4 (*c* 0.95, $CHCl_3$); ν_{max} (ATR) 3404 m, 3234 m, 2957 m, 2921 m, 2872 m, 1733 s, 1682 s and 1651 m cm^{-1}; δ_H ($CDCl_3$) 0.76 (3H, d, *J* 7.0 Hz, CH_3), 0.90 (3H, d, *J* 7.0 Hz, CH_3), 0.92 (3H, d, *J* 6.5 Hz, CH_3), 1.0–1.3 (1H, m, CH), 1.4–2.1 (8H, m, 3×CH_2, 2×CH), 4.84 (1H, td, *J* 11.0 and 4.5 Hz, CHO), 5.84 (1H, br, NH_2), 6.95 (1H, br, NH_2); δ_C ($CDCl_3$) 160.0 (C=O), 158.9 (C=O), 78.5 (CHO), 47.2 (CH), 40.7 (CH_2), 34.4 (CH_2), 31.9 (CH), 26.7 (CH), 24.0 (CH_2), 22.1 (CH_3), 20.9 (CH_3), 16.6 (CH_3); *m/z* (ESI) 245 ($M+NH_4^+$, 30), 139 (20), 122 (18). Found (ESI) 245.1864; $C_{12}H_{25}N_2O_3$ ($M+NH_4^+$) requires 245.1864.

4.2.11. (*S*)-Glycerol acetonide oxamide 12d. To a stirred mixture of sodium hydride in mineral oil (0.02 g, 0.56 mmol) and (*S*)-glycerol acetonide (0.10 g, 0.56 mmol) in THF (20 mL) at 0 °C, oxalyl chloride (0.14 g, 1.12 mmol) was added dropwise. The ice bath was removed and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue dried on a vacuum line. The crude oxalic ester was redissolved in CH_2Cl_2 (2 mL), and concentrated aqueous ammonia (0.20 mL excess) was added at 0 °C. The mixture was stirred for 30 min, then water was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give compound **12d** (82 mg, 72%) as a white solid. Mp 184–186 °C (decomp.); $[\alpha]_D^{20}$ −18.0 (*c* 0.05, $CHCl_3$); ν_{max} (ATR) 3391 m, 3131 s, 3043 s, 1737 m, 1690 s and 1607 m cm^{-1}; δ_H ($CDCl_3$) 1.33 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.80 (1H, dd, *J* 8.7 and 5.4 Hz, OCH_2), 4.08 (1H, dd, *J* 8.7 and 6.4 Hz, OCH_2), 4.2–4.5 (3H, m, OCH), 6.32 (1H, br, NH_2) 7.00 (1H, br, NH_2); δ_C ($CDCl_3$) 160.0 (C=O), 158.3 (C=O), 110.2 ($OCMe_2$), 73.0 (OCH), 67.0 (OCH_2), 66.3 (OCH_2), 26.7 (CH_3), 25.3 (CH_3); *m/z* (ESI) 221 ($M+NH_4^+$, 30), 204 (MH^+, 100), 163 (70), 146 (50), 101 (95). Found (ESI) 221.1133; $C_8H_{17}N_2O_5$ ($M+NH_4^+$) requires 221.1132.

4.2.12. (*R*)-1-(Carboxyethyl)ethyl cyanoformate 10a. To a solution of oxamide **12a** (0.8 g, 4.2 mmol) and pyridine (1.4 mL, 16.9 mmol) in CH_2Cl_2 (15 mL), TFAA (0.7 mL, 5.0 mmol) was added dropwise at 0 °C. The ice bath was removed and the solution was stirred for 2 h at room temperature. Water was added and the layers were separated. The organic layer was washed with water (20 mL) and then with dilute hydrochloric acid (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo

to leave compound **10a** (0.57 g, 78%) as a yellow oil. $[\alpha]_D^{20}$ −40.3 (*c* 1.2, $CHCl_3$); ν_{max} (CH_2Cl_2) 2989 s, 2945 m, 2249 m and 1748 s cm^{-1}; δ_H ($CDCl_3$) 1.27 (3H, t, *J* 7.1 Hz, CH_3CH_2), 1.58 (3H, d, *J* 7.1 Hz, CH_3CH), 4.21 (2H, q, *J* 7.1 Hz, OCH_2), 5.20 (1H, q, *J* 7.1 Hz, CH_3CHO); δ_C ($CDCl_3$) 168.1 (C=O), 143.8 (C=O), 109.3 (CN), 73.0 (OCH), 62.6 (OCH_2), 16.8 (CH_3), 14.3 (CH_3); *m/z* (EI) 171 (M^+, 55%), 98 (50), 73 (60), 54 (90), 43 (100). Found (ESI) 285.0948 and 263.1111; $C_{11}H_{18}O_7Na$ $(2M-2CN-CO+Na)^+$ requires 285.0950 and $C_{11}H_{19}O_7$ $(2M-2CN-CO+H)^+$ requires 263.1131.

4.2.13. (*R*)-1-(Carboxyethyl)benzyl cyanoformate 10b. To a solution of oxamide **12b** (1.1 g, 4.2 mmol) and pyridine (1.4 mL, 16.9 mmol) in CH_2Cl_2 (15 mL), TFAA (0.7 mL, 5.0 mmol) was added dropwise at 0 °C. The ice bath was removed and the solution was stirred for 2 h at room temperature. Water was added and the layers were separated. The organic layer was washed with water (20 mL) and then with dilute hydrochloric acid (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to leave compound **10b** (0.87 g, 87%) as a yellow oil. $[\alpha]_D^{20}$ −8.4 (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3069 s, 3038 w, 2986 m, 2943 m, 2908 w, 2249 m, 1791 s and 1748 s cm^{-1}; δ_H ($CDCl_3$) 1.23 (3H, t, *J* 7.1 Hz, CH_3CH_2), 4.1–4.3 (2H, m, OCH_2), 6.05 (1H, s, PhCHO), 7.3–7.5 (5H, m, ArH); δ_C ($CDCl_3$) 166.6 (C=O), 143.8 (C=O), 138.8 (ArC), 129.6 (ArCH), 128.1 (ArCH), 126.9 (ArCH), 109.1 (CN), 78.3 (OCH), 62.8 (OCH_2), 14.2 (CH_3); *m/z* (EI) 233 (M^+, 1%), 160 (90), 105 (100). Found (EI) 233.0685; $C_{12}H_{11}NO_4$ (M^+) requires 233.0683.

4.2.14. (+)-Menthyl cyanoformate 10c.[38] To a solution of oxamide **12c** (0.5 g, 2.2 mmol) and pyridine (0.7 g, 8.8 mmol) in CH_2Cl_2 (8 mL), TFAA (0.55 g, 2.6 mmol) was added dropwise at 0 °C. The ice bath was removed, and the solution was stirred for 2 h at room temperature. Water was added and the layers were separated. The organic layer was washed with water (20 mL), then with dilute hydrochloric acid (20 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to leave compound **10c** (0.44 g, 96%) as a yellow oil. $[\alpha]_D^{20}$ +78.5 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2960 s, 2873 s, 2244 m and 1744 s cm^{-1}; δ_H ($CDCl_3$) 0.70 (3H, d, *J* 7.0 Hz, CH_3), 0.86 (3H, d, *J* 7.0 Hz, CH_3), 0.87 (3H, d, *J* 6.5 Hz, CH_3), 0.9–1.2 (3H, m, 3×CyCH), 1.3–1.5 (2H, m, 2×CyCH), 1.6–1.7 (2H, m, 2×CyCH), 1.7–1.9 (1H, m, CyCH), 1.9–2.0 (1H, m, CyCH), 4.80 (1H, td, *J* 11.0 and 4.5 Hz, CHO); δ_C ($CDCl_3$) 144.3 (CO), 109.9 (CN), 81.2 (OCH), 47.1 (CH), 40.6 (CH_2), 34.4 (CH_2), 31.9 (CH), 26.8 (CH), 23.9 (CH_2), 22.0 (CH_3), 20.8 (CH_3), 16.5 (CH_3); *m/z* (CI) 232 $(M-CN+OMe+NH_4^+$, 30), 172 (100), 155 (40), 137 (50), 95 (60). Found (ESI) 384.3110; $C_{22}H_{42}NO_4$ $(2M-2CN+NH_4^+)$ requires 384.3108.

4.2.15. (*S*)-Glycerol acetonide cyanoformate 10d. To a solution of oxamide **12d** (0.86 g, 4.2 mmol) and pyridine (1.4 mL, 16.9 mmol) in CH_2Cl_2 (15 mL), TFAA (0.7 mL, 5.0 mmol) was added dropwise at 0 °C. The ice bath was removed and the solution was stirred for 2 h at room temperature. Water was added and the layers were separated. The organic layer was washed with water (20 mL) and then with dilute hydrochloric acid (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to leave compound **10d** (0.16 g, 21%) as a yellow oil. $[\alpha]_D^{20}$ +1.4 (*c* 1.15, $CHCl_3$); ν_{max} (neat) 2991 w, 2248 w, 1791 m and 1755 s cm^{-1}; δ_H ($CDCl_3$) 1.34 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.76 (1H, dd, *J* 8.6 and 4.9 Hz, OCH_2), 4.08 (1H, dd, *J* 8.6 and 6.1 Hz, OCH_2), 4.2–4.4 (3H, m, OCH+OCH_2); δ_C ($CDCl_3$) 144.3 (CO_2), 110.8 (CMe_2), 109.3 (CN), 73.1 (OCH), 68.7 (OCH_2), 64.8 (OCH_2), 26.9 (CH_3), 25.5 (CH_3); *m/z* (CI) 336 $(2M-2CN+NH_4^+$, 20), 294 (100), 277 (50), 232 (70). Found (ESI) 336.1651; $C_{14}H_{26}NO_8$ $(2M-2CN+NH_4^+)$ requires 336.1653.

4.3. Asymmetric addition of achiral cyanoformates to aldehydes in the presence of potassium cyanide

To a stirred solution of aldehyde (9.4 mmol) and catalyst **1** (229 mg, 0.2 mmol) in CH_2Cl_2 (25 mL) was added KCN (61 mg, 0.9 mmol). The mixture was cooled to −40 °C, then the cyanoformate (11.3 mmol) was added and the reaction mixture was stirred vigorously at −40 °C for 24 h. The reaction mixture was warmed to room temperature and passed through a plug of silica gel, eluting with CH_2Cl_2. The solvent was removed in vacuo to give the cyanohydrin carbonates **13a–g** or **14a–f** as a yellow oil.

4.3.1. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 13a.[10b,18,28a] Compound **13a** was obtained in quantitative yield. $[\alpha]_D^{20}$ −16.5 (*c* 1.0, $CHCl_3$) [lit.[28a] $[\alpha]_D^{20}$ +16.2 (*c* 2.8, $CHCl_3$) for (*R*)-enantiomer with 94% ee]. Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=117.2 and 119.5 min.

4.3.2. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile 13b.[18] Compound **13b** was obtained in 98% yield. $[\alpha]_D^{20}$ +1.8 (*c* 1.35, $CHCl_3$) [lit.[18] $[\alpha]_D^{20}$ +1.8 (*c* 1.8, $CHCl_3$) for (*S*)-enantiomer with 95% ee]. Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=242.2 and 245.7 min.

4.3.3. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)acetonitrile 13c.[18] Compound **13c** was obtained in quantitative yield. $[\alpha]_D^{20}$ −9.9 (*c* 1.4, $CHCl_3$). Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.4 °C/min; t_R=79.4 and 82.6 min.

4.3.4. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 13d.[18,28b,c] Compound **13d** was obtained in 94% yield. $[\alpha]_D^{20}$ +21.9 (*c* 1.1, $CHCl_3$) [lit.[18] $[\alpha]_D^{20}$ −23.4 (*c* 1.9, $CHCl_3$) for (*S*)-enantiomer with 94% ee. Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=250.1 and 254.2 min.

4.3.5. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile 13e.[18] Compound **13e** was obtained in 90% yield. $[\alpha]_D^{20}$ −42.8 (*c* 1.05, $CHCl_3$). Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=140.6 and 143.3 min.

4.3.6. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexyl-acetonitrile 13f.[18,28c] Compound **13f** was obtained in 86% yield. $[\alpha]_D^{20}$ −42.1 (*c* 1.05, $CHCl_3$) [lit.[28c] $[\alpha]_D^{20}$ +53.4 (*c* 2.0, $CHCl_3$) for (*R*)-enantiomer with 96% ee]. Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=97.8 and 99.1 min.

4.3.7. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 13g.[18,28c] Compound **13g** was obtained in 79% yield. $[\alpha]_D^{20}$ −68.0 (*c* 1.35, $CHCl_3$) [lit.[28c] $[\alpha]_D^{20}$ +75.6 (*c* 2.2, $CHCl_3$) for (*R*)-enantiomer with 87% ee]. Chiral GC conditions: flow rate 1 mL/min, initial temperature 50 °C, held at initial temperature for 2 min, then ramp rate 0.1 °C/min; t_R=150.7 and 157.7 min.

4.3.8. *O*-Methoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 14a.[27a,40,44] Compound **14a** was obtained in 92% yield. $[\alpha]_D^{20}$ −15.7 (*c* 1.15, $CHCl_3$). Chiral GC conditions: flow rate 1 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=99.7 and 103.0 min.

4.3.9. *O*-Benzyloxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 14b.[27a] Compound **14b** was obtained in 100% yield. $[\alpha]_D^{20}$ −17.4 (*c* 1.2, $CHCl_3$); ν_{max} (neat) 2985 s, 2245 m and 1756 s cm^{-1}; δ_H ($CDCl_3$) 5.0–5.3 (2H, m, OCH_2), 6.18 (1H, s, CHCN), 7.2–7.5 (10H, m, ArH); δ_C ($CDCl_3$) 153.8 (CO_3), 131.1 (ArC), 130.0 (ArC), 129.7 (ArCH), 129.5 (ArCH), 129.4 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 128.3 (ArCH), 116.1 (CN), 71.5 (OCH), 67.0 (OCH_2); *m/z* (EI) 267 (M^+, 3%), 191 (5), 117 (100). Found (ESI) 290.07807; $C_{16}H_{13}NO_3Na$ (M+Na^+) requires 290.07876.

4.3.10. *O-tert*-Butyloxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 14c.[32b] Compound **14c** was obtained in 100% yield. $[\alpha]_D^{20}$ −14.2 (*c* 1.25, $CHCl_3$); *m/z* (EI) 233 (M^+, 6%), 177 (60), 133 (15), 116 (100), 77 (10), 57 (96).

4.3.11. *O*-Methoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 14d.[40] Compound **14d** was obtained in 85% yield. $[\alpha]_D^{20}$ −74.1 (*c* 1.2, $CHCl_3$); *m/z* (EI) 171 (M^+, 3%), 156 (10), 112 (15), 96 (20), 57 (100). Chiral GC conditions: flow rate 1 mL/min, initial temperature 70 °C, held at initial temperature for 2 min, then ramp rate 0.1 °C/min; t_R=35.4 and 36.7 min.

4.3.12. *O*-Benzyloxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 14e. Compound **14e** was obtained in 100% yield. $[\alpha]_D^{20}$ −40.9 (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2970 s, 2245 w and 1755 s cm^{-1}; δ_H ($CDCl_3$) 1.12 (9H, s, $(CH_3)_3$), 4.94 (1H, s, CHCN), 5.2–5.3 (2H, m, CH_2O), 7.3–7.5 (5H, m, ArH); δ_C ($CDCl_3$) 154.4 (CO_3), 134.7 (ArC), 129.4 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 116.1 (CN), 73.9 (CHO), 71.3 (CH_2O), 35.3 (CMe_3), 25.5 ($(CH_3)_3$); *m/z* (EI) 247 (M^+, 43%), 161 (100). Found (CI) 265.1546; $C_{14}H_{21}N_2O_3$ (M+NH_4)$^+$ requires 265.1547.

4.3.13. *O-tert*-Butyloxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 14f. Compound **14f** was obtained in 100% yield. $[\alpha]_D^{20}$ −55.3 (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2975 s, 2242 w and 1752 s cm^{-1}; δ_H ($CDCl_3$) 1.03 (9H, s, $(CH_3)_3$), 1.44 (9H, s, $(CH_3)_3$), 4.81 (1H, s, CHO); δ_C ($CDCl_3$) 152.5 (CO_3), 116.4 (CN), 84.5 (OCH), 72.7 ($OCMe_3$), 35.2 (CMe_3), 28.0 ($(CH_3)_3$), 25.5 ($(CH_3)_3$); *m/z* (CI) 214 (MH^+, 100%), 196 (23), 113 (59), 96 (93), 59 (82), 41 (53). Found (ESI) 236.1256; $C_{11}H_{19}NO_3Na$ (M+Na^+) requires 236.1257. Chiral GC conditions: flow rate 1 mL/min, initial temperature 70 °C, held at initial temperature for 2 min, then ramp rate 0.1 °C/min; t_R=73.4 and 74.9 min.

4.4. Diastereoselective synthesis of cyanoformates derived from chiral cyanoformates 6a,b

To a stirred solution of aldehyde (benzaldehyde or pivaldehyde) (2.4 mmol) and catalyst **1** (57.8 mg, 0.05 mmol) in CH_2Cl_2 (6 mL) was added KCN (7.7 mg, 0.1 mmol). The mixture was cooled to −78 °C, then cyanoformate **6a** or **6b** (0.5 g, 2.9 mmol) was added and the reaction mixture was stirred vigorously at −40 °C for 24 h. If after this time, the reaction had not reached completion an additional batch of KCN (7.7 mg, 0.1 mmol) and catalyst **1** (57.8 mg, 0.05 mmol) was added and the reaction mixture was stirred at −40 °C for a further 48 h. The reaction mixture was warmed to room temperature and passed through a plug of silica gel, eluting with CH_2Cl_2. The solvent was removed in vacuo to give the product.

4.4.1. Compounds 15a (major) and 16a (minor). Compounds **15a** and **16a** were obtained as a colourless, crystalline solid (0.48 g, 88% conversion from benzaldehyde). To obtain crystals suitable for X-ray analysis, the white solid was first further purified by flash chromatography (CH_2Cl_2) and then recrystallised from CH_2Cl_2. $[\alpha]_D^{20}$ +36.8 (*c* 1.45, $CHCl_3$); ν_{max} (neat) 2985 m, 2346 w and 1762 s cm^{-1}; δ_H ($CDCl_3$) **15a**: 1.51 (3H, d, *J* 6.7 Hz, CH_3), 5.68 (1H, q, *J* 6.7 Hz, CHMe), 6.15 (1H, s, CHCN), 7.2–7.8 (10H, m, ArH); **16a** (not all peaks visible): 6.10 (1H, s, CH); δ_C ($CDCl_3$) **15a**: 153.3 (CO_3), 140.5 (ArC), 131.8 (ArC), 131.1 (ArCH), 129.7 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 128.4 (ArCH), 126.5 (ArCH), 116.23 (CN), 78.9 (Ph*C*HCN), 66.9 (PhCHO), 22.6 (CH_3); *m/z* (CI) 282 (MH^+, 2%), 238 (7), 193 (10), 105 (100). Found (ESI) 304.0945; $C_{17}H_{15}NO_3Na$ (M+Na^+) requires 304.0944.

4.4.2. Compounds 15b (major) and 16b (minor). Compounds **15b** and **16b** were obtained as a white solid (0.59 g, 100% conversion from pivaldehyde). To obtain crystals suitable for X-ray analysis, the white solid was first further purified by flash chromatography (CH_2Cl_2) and then recrystallised from CH_2Cl_2. $[\alpha]_D^{20}$ +33.3 (*c* 1.15, $CHCl_3$); ν_{max} (KBr) 2973 s, 2244 w and 1754 s cm^{-1}; δ_H ($CDCl_3$) **15b**: 1.02 (9H, s, $(CH_3)_3$), 1.55 (3H, d, *J* 6.6 Hz, CH_3), 4.85 (1H, s, CHCN), 5.69 (1H, q, *J* 6.6 Hz, CHMe), 7.2–7.4 (5H, m, ArH); **16b** (not all peaks visible): 4.79 (1H, s, CH); δ_C ($CDCl_3$) 153.8 (CO_3), 140.4 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 115.9 (CN), 78.5 (*C*HCN), 73.6 (CHMe), 35.4 (CMe_3), 25.5 ($(CH_3)_3$), 22.5 (CH_3); *m/z* (EI) 261 (M^+, 27%), 121 (41), 105 (100). Found (ESI) 284.1257; $C_{15}H_{19}NO_3Na$ (M+Na^+) requires 284.1257.

4.4.3. Compounds 17a (major) and 18a (minor). Compounds **17a** and **18a** were obtained as a yellow oil (0.53 g, 66% conversion from benzaldehyde). $[\alpha]_D^{20}$ −40.1 (*c* 2.75, $CHCl_3$); ν_{max} (neat) 2986 m, 2348 w and 1761 s cm^{-1}; δ_H

($CDCl_3$) **17a**: 1.52 (3H, d, *J* 6.5 Hz, CH_3), 5.70 (1H, q, *J* 6.5 Hz, CHMe), 6.11 (1H, s, CHCN), 7.2–7.8 (10H, m, Ar*H*); **18a** (not all peaks visible): 6.15 (1H, s, CH); δ_C ($CDCl_3$) 153.3 (CO_3), 140.4 (ArC), 131.5 (ArC), 131.0 (ArCH), 129.6 (ArCH), 129.1 (ArCH), 129.0 (ArCH), 128.2 (ArCH), 126.5 (ArCH), 116.2 (CN), 78.9 (*C*HCN), 66.8 (CHPh), 22.6 (CH_3); *m*/*z* (CI) 282 (MH^+, 4%), 105 (100). Found (ESI) 304.0956; $C_{17}H_{15}NO_3Na$ $(M+Na)^+$ requires 304.0944.

4.4.4. Compounds 17b (major) and 18b (minor). Compounds **17b** and **18b** were obtained as a yellow oil (0.37 g, 100% conversion from pivaldehyde). $[\alpha]_D^{20}$ −115.2 (*c* 1.25, $CHCl_3$); ν_{max} (neat) 2972 s, 2227 w and 1753 s cm^{-1}; δ_H ($CDCl_3$) **17b**: 1.10 (9H, s, $(CH_3)_3$), 1.65 (3H, d, *J* 6.6 Hz, CH_3), 4.89 (1H, s, CHCN), 5.79 (1H, q, *J* 6.6 Hz, CHMe), 7.3–7.4 (5H, m, ArH); **18b**: 4.96 (1H, s, CH); δ_C ($CDCl_3$) 153.8 (CO_3), 140.8 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 116.2 (CN), 78.5 (*C*HCN), 73.6 (CHMe), 25.5 ($(CH_3)_3$), 22.6 (CH_3); *m*/*z* (EI) 261 (M^+, 16%), 121 (33), 105 (100). Found (ESI) 284.1251; $C_{15}H_{19}NO_3Na$ $(M+Na)^+$ requires 284.1257.

4.5. Diastereoselective synthesis of cyanoformates derived from chiral cyanoformates 10a–d

To a stirred solution of KCN (3.3 mg, 0.06 mmol) and catalyst **1** (31.2 mg, 0.027 mmol) at −40 °C were added aldehyde (1.28 mmol) and cyanoformate **10a**–**d** (1.54 mmol). The reaction mixture was stirred at −40 °C for 24 h and if no reaction occurred, the mixture was allowed to warm to room temperature and stirred for an additional two weeks. The reaction mixture was passed through a plug of silica gel, eluting with CH_2Cl_2. The sample was purified by flash chromatography (CH_2Cl_2) to give compounds **19a**,**b** or **20a**,**b** as white solids.

4.5.1. Compounds 19a and 19b. Compounds **19a** and **19b** were obtained in a 12.3:1 ratio in favour of **19a** using the (*R*,*R*)-enantiomer of catalyst **1** and in a 9:1 ratio in favour of **19b** using the (*S*,*S*)-enantiomer of catalyst **1**. $[\alpha]_D^{20}$ **19a**: +112 (*c* 0.05, $CHCl_3$), **19b**: −12.5 (*c* 0.8, $CHCl_3$); ν_{max} (neat) 2988 m and 1748 s cm^{-1}; δ_H ($CDCl_3$) **19a**: 1.22 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.56 (3H, d, *J* 7.2 Hz, C*H*$_3$CH), 4.19 (2H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$O), 5.07 (1H, q, *J* 7.2 Hz, CH$_3$C*H*O), 6.28 (1H, s, CHCN), 7.4–7.7 (5H, m, ArH); **19b**: 1.27 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.51 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 4.1–4.3 (2H, m, CH$_3$C*H*$_2$O), 5.01 (1H, q, *J* 7.1 Hz, CH$_3$C*H*O), 6.25 (1H, s, CHCN), 7.4–7.6 (5H, m, ArH); δ_C ($CDCl_3$) **19a**: 169.5 (CO_2), 153.1 (CO_3), 131.5 (ArC), 130.7 (ArCH), 129.5 (ArCH), 125.9 (ArCH), 115.4 (CN), 73.2 (OCH), 66.9 (OCH), 61.7 (OCH_2), 16.8 (CH_3), 13.9 (CH_3); **19b**: 169.4 (CO_2), 152.9 (CO_3), 131.6 (ArC), 130.8 (ArCH), 129.6 (ArCH), 126.1 (ArCH), 115.3 (CN), 73.3 (OCH), 67.0 (OCH), 61.8 (OCH_2), 16.8 (CH_3), 14.0 (CH_3); *m*/*z* (CI) 295 ($M+NH_4^+$, 40), 136 (100). Found (ESI) 295.1292; $C_{14}H_{19}N_2O_5$ $(M+NH_4)^+$ requires 295.1288.

4.5.2. Compounds 20a and 20b. Compounds **20a** and **20b** were obtained in a 10.8:1 ratio in favour of **20a** using the (*R*,*R*)-enantiomer of catalyst **1** and in a 13.3:1 ratio in favour of **20b** using the (*S*,*S*)-enantiomer of catalyst **1**. Mp **20a**: 82–84 °C, **20b**: 89–91 °C; $[\alpha]_D^{20}$ **20a**: +34.0 (*c* 0.1, $CHCl_3$), **20b**: +100 (*c* 0.05, $CHCl_3$); ν_{max} (ATR) 2988 m, 1761 m, 1744 and 1633 s cm^{-1}; δ_H ($CDCl_3$) **20a**: 1.13 (9H, s, $(CH_3)_3$), 1.26 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.54 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 4.19 (2H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$O), 4.98 (1H, s, CHCN), 5.02 (1H, q, *J* 7.1 Hz, CH$_3$C*H*O); **20b**: 1.12 (9H, s, $(CH_3)_3$), 1.30 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.57 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 4.1–4.3 (2H, m, CH$_3$C*H*$_2$O), 4.92 (1H, s, CHCN), 5.05 (1H, q, *J* 7.1 Hz, CH$_3$C*H*O); δ_C ($CDCl_3$) **20a**: 169.7 (CO_2), 153.5 (CO_3), 115.4 (CN), 73.8 (CHO), 73.1 (CHO), 62.0 (OCH_2), 35.1 (CMe_3), 25.2 (CH_3), 17.0 (CH_3), 14.1 (CH_3); **20b**: 169.4 (CO_2), 153.4 (CO_3), 115.3 (CN), 73.9 (CHO), 73.2 (CHO), 61.8 (OCH_2), 35.0 (CMe_3), 25.1 (CH_3), 16.8 (CH_3), 14.0 (CH_3); *m*/*z* (ESI) 280 ($M+Na^+$, 80%), 275 ($M+NH_4^+$, 100), 258 (MH^+, 10), 241 (20). Found (ESI) 275.1600; $C_{12}H_{23}N_2O_5$ $(M+NH_4)^+$ requires 275.1601.

4.6. Asymmetric addition of ethyl cyanoformate to aldehydes in the presence of potassium cyanide/18-crown-6 complex

KCN/18-crown-6 complex[41] (6.6 mg, 0.02 mmol) and catalyst **1** (36 mg, 0.03 mmol) were dissolved in CH_2Cl_2 (5 mL). The solution was cooled to −40 °C, then aldehyde (2.0 mmol) and ethyl cyanoformate (0.24 mL, 2.4 mmol) were added. The resulting solution was allowed to stir for 24 h (or 48 h when specified) at −40 °C. The reaction mixture was warmed to room temperature and passed through a plug of silica gel, eluting with CH_2Cl_2. The solvent was removed in vacuo to give the product as a yellow oil.

4.6.1. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 13a.[10b,18,28a] Compound **13a** was obtained in quantitative yield. Analytical data as reported in Section 4.3.1.

4.6.2. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile 13b.[18] Compound **13b** was obtained in quantitative yield. Analytical data as reported in Section 4.3.2.

4.6.3. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 13d.[18,28b,c] Compound **13d** was obtained in quantitative yield after a reaction time of 48 h. Analytical data as reported in Section 4.3.4.

4.6.4. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile 13e.[18] Compound **13e** was obtained in 98% yield. Analytical data as reported in Section 4.3.5.

4.6.5. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexyl-acetonitrile 13f.[18,28c] Compound **13f** was obtained in quantitative yield. Analytical data as reported in Section 4.3.6.

4.6.6. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 13g.[18,28c] Compound **13g** was obtained in quantitative yield. Analytical data as reported in Section 4.3.7.

4.6.7. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methylphenyl)acetonitrile 13h.[45] Compound **13h** was obtained in quantitative yield. $[\alpha]_D^{20}$ −21.5 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2986 m, 1756 s and 1697 w cm^{-1}; δ_H ($CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 2.44 (3H, s, ArCH_3), 4.2–4.4 (2H, m, OCH_2), 6.38 (1H, s, CHCN), 7.2–7.4 (3H, m, ArH), 7.56 (1H, dd, *J* 7.5 and 1.3 Hz, ArH); δ_C ($CDCl_3$) 153.8 (CO_3),

137.1 (ArC), 131.7 (ArCH), 130.9 (ArCH), 130.1 (ArC), 128.9 (ArCH), 127.1 (ArCH), 115.9 (CN), 65.8 (*C*HCN), 65.0 (CH_2O), 19.1 (CH_3), 14.4 (CH_3); *m/z* (EI) 219 (M^+, 5%), 130 (40), 129 (100). Found (EI) 219.0813; $C_{12}H_{13}NO_3$ (M^+) requires 219.0890. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=146.7 and 147.0 min.

4.6.8. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methylphenyl)acetonitrile 13i.[18] Compound **13i** was obtained in quantitative yield. $[\alpha]_D^{20}$ −1.9 (*c* 1.55, $CHCl_3$). Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=118.7 and 121.3 min.

4.6.9. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methoxyphenyl)acetonitrile 13j.[18] Compound **13j** was obtained in quantitative yield. $[\alpha]_D^{20}$ +2.8 (*c* 1.0, $CHCl_3$). Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=207.6 and 224.9 min.

4.6.10. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)acetonitrile 13k.[18] Compound **13k** was obtained in quantitative yield. $[\alpha]_D^{20}$ −4.9 (*c* 1.65, $CHCl_3$). Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=223.4 and 227.9 min.

4.6.11. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-chlorophenyl)acetonitrile 13l.[46] Compound **13l** was obtained in quantitative yield. $[\alpha]_D^{20}$ −10.1 (*c* 1.05, $CHCl_3$); ν_{max} (neat) 3074 s, 2986 s, 2941 s, 2868 s and 1763 s cm^{-1}; δ_H ($CDCl_3$) 1.35 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 4.2–4.4 (2H, m, OCH_2), 6.62 (1H, s, CHCN), 7.3–7.5 (3H, m, ArH), 7.7–7.8 (1H, m, ArH); δ_C ($CDCl_3$) 153.5 (CO_3), 133.9 (ArC), 132.1 (ArCH), 130.6 (ArCH), 129.9 (ArCH), 129.8 (ArC), 128.0 (ArCH), 115.3 (CN), 66.0 (OCH_2), 64.0 (CHO), 14.4 (CH_3); *m/z* (CI) 259 ((^{37}Cl)M+NH_4^+, 35%), 257 ((^{35}Cl)M+NH_4^+, 100%), 171 (20), 169 (60). Found (CI) 257.0687; $C_{11}H_{14}N_2O_3$(^{35}Cl) $(M+NH_4)^+$ requires 257.0687. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 2 °C/min; t_R=41.0 and 42.0 min.

4.6.12. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-chlorophenyl)acetonitrile 13m.[18] Compound **13m** was obtained in quantitative yield. $[\alpha]_D^{20}$ −2.6 (*c* 0.94, $CHCl_3$) [lit.[18] $[\alpha]_D^{20}$ −2.9 (*c* 1.3, $CHCl_3$)]. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=123.4 and 124.2 min.

4.6.13. *O*-Ethoxycarbonyl (*S*,*E*)-2-hydroxy-pent-3-enonitrile 13n.[43] Compound **13n** was obtained in quantitative yield. $[\alpha]_D^{20}$ +6.6 (*c* 1.0, $CHCl_3$) [lit.[43a] $[\alpha]_D^{25}$ −12.8 (*c* 1.4, $CHCl_3$) for (*R*)-enantiomer]; *m/z* (CI) 187 (M+NH_4^+, 100%). Found (CI) 187.1077; $C_8H_{15}N_2O_3$ $(M+NH_4)^+$ requires 187.1077. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=22.6 and 24.4 min.

4.6.14. *O*-Ethoxycarbonyl (*S*,*E*)-2-hydroxy-hex-3-enonitrile 13o. Compound **13o** was obtained in quantitative yield. $[\alpha]_D^{20}$ +8.6 (*c* 4.5, $CHCl_3$); ν_{max} (neat) 2971 w, 2879 w and 1758 s cm^{-1}; δ_H ($CDCl_3$) 1.06 (3H, t, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.27 (3H, t, *J* 7.3 Hz, C*H*$_3$CH$_2$O), 2.0–2.2 (2H, m, CH$_3$C*H*$_2$CH=), 4.19 (2H, q, *J* 7.3 Hz, OCH_2), 5.4–5.6 (2H, m, =CHCHCN), 6.18 (1H, dt, *J* 15.3 and 6.3 Hz, =C*H*CH$_2$); δ_C ($CDCl_3$) 152.5 (CO_3), 141.4 (=CH), 118.3 (=CH), 114.4 (CN), 64.3 (OCH_2), 64.0 (OCH), 24.1 (=CH*C*H$_2$), 13.1 (CH_3), 11.5 (CH_3); *m/z* (CI) 201 (M+NH_4^+, 60%), 113 (100), 102 (50). Found (ESI) 206.0789; $C_9H_{13}NO_3Na$ $(M+Na)^+$ requires 206.0787. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=36.2 and 37.4 min.

4.6.15. *O*-Ethoxycarbonyl (*S*,*E*)-2-hydroxy-3-methyl-pent-3-enonitrile 13p. Compound **13p** was obtained in quantitative yield after a 48 h reaction. $[\alpha]_D^{20}$ +7.7 (*c* 1.8, $CHCl_3$); ν_{max} (neat) 2986 s, 2950 s, 2921 s, 2484 w, 1756 s and 1670 s cm^{-1}; δ_H ($CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.66 (3H, d, *J* 7.0 Hz, C*H*$_3$CH=), 1.76 (3H, s, CH$_3$C=), 4.1–4.3 (2H, m, OCH_2), 5.55 (1H, s, CHCN), 5.87 (1H, q, *J* 7.0 Hz, =C*H*CH$_3$); δ_C ($CDCl_3$) 153.6 (CO_3), 130.2 (=CH), 127.1 (=C), 115.6 (CN), 70.1 (*C*HCN), 64.5 (OCH_2), 14.2 (CH_3), 13.7 (CH_3), 12.3 (CH_3); *m/z* (CI) 201 (M+NH_4^+, 70%), 113 (100). Found (CI) 201.1233; $C_9H_{17}N_2O_3$ $(M+NH_4)^+$ requires 201.1234. Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, held at initial temperature for 2 min, then ramp rate 0.2 °C/min; t_R=32.2 and 33.6 min.

4.7. Conversion of (*S*)-cyanohydrin carbonates into γ-substituted nitriles

4.7.1. (*S*)-4-Azido-pent-2-enonitrile 21.[43] A solution of cyanohydrin carbonate **13n** (2.0 g, 11.8 mmol) and sodium azide (1.54 g, 23.6 mmol) in THF (30 mL) and water (30 mL) was cooled in an ice bath and stirred under a nitrogen atmosphere. Tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.28 mmol) was added, the solution was allowed to warm to room temperature and stirred for 16 h. Et_2O (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was passed through a plug of silica topped with $MgSO_4$, eluting with Et_2O. The eluent was evaporated in vacuo and the residue was purified by silica gel chromatography ($CHCl_3$) to give compound **21** (1.17 g, 81%) as a colourless oil. $[\alpha]_D^{20}$ −38.5 (*c* 1.05, $CHCl_3$) [lit.[43a] $[\alpha]_D^{20}$ −38.7 (*c* 1.9, $CHCl_3$) for (*R*)-enantiomer with 81% ee].

4.7.2. (*S*)-4-Amino-pentanonitrile 22. Azide **21** (0.25 g, 2.0 mmol) was dissolved in dry methanol (150 mL) and 10% Pd/C (0.04 g) was added. The reaction mixture was stirred under a hydrogen atmosphere for 4 days, then filtered through a plug of silica and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography (MeOH) to give compound **22** (50 mg, 17%) as a colourless oil. Compound **22** was found to be unstable and so was characterised as its *N*-benzoyl derivative.

4.7.3. *N*-Benzoyl (*S*)-4-amino-pentanonitrile 23. To a stirred solution of amine **22** (50 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.12 g, 1.2 mmol) and benzoyl chloride (0.17 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 16 h, then the solvent was evaporated in vacuo and the residue was purified by silica gel chromatography ($CHCl_3$) to give compound **23** (0.09 g, 81%) as a yellow oil. δ_H ($CDCl_3$) 1.42 (3H, d, *J* 6.7 Hz, C*H*$_3$CH), 1.8–1.9 (2H, m, C*H*$_2$CH$_2$CN), 2.39 (2H, t, *J* 7.5 Hz, CH_2CN), 4.1–4.3 (1H, m, C*H*NH), 6.67 (1H, br, NH), 7.3–7.8 (5H, m, ArH). Chiral GC conditions: flow rate 1.6 mL/min, initial temperature 100 °C, ramp rate 2 °C/min; t_R=9.6 and 12.3 min.

4.8. Kinetics of the addition of ethyl cyanoformate to benzaldehyde catalysed by complex 1 and potassium cyanide/18-crown-6

To a stirred solution of catalyst **1**, KCN/18-crown-6 complex and ethyl cyanoformate (0.2 g, 2.0 mmol) in CH_2Cl_2 at 20 °C, benzaldehyde (0.106 g, 1.0 mmol) was added. Samples (0.5 mL) were taken at regular intervals and passed through a plug of silica. The solvent was evaporated in vacuo, and the residue was redissolved in $CDCl_3$ and analysed by ^{1}H NMR spectroscopy. The extent of reaction was determined from the relative integrals of the PhC*H*O signals of unreacted benzaldehyde and mandelonitrile ethyl carbonate.

4.9. Supplementary information

Crystallographic data (excluding structural factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 624637 and 624638. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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