Cyanide ion cocatalysis in Ti(salen) catalysed asymmetric cyanohydrin carbonate synthesis†

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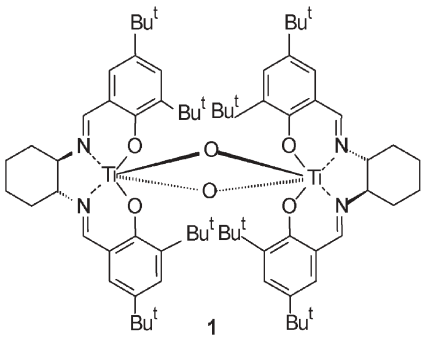
In the presence of potassium cyanide or the potassium cyanide/18-crown-6 complex as a cocatalyst, 1–2 mol% of titanium(salen) complex 1 catalyses the asymmetric addition of achiral cyanoformates to aldehydes, giving cyanohydrin carbonates with high enantiomeric excesses; and catalyses the diastereoselective addition of chiral cyanoformates derived from α-methylbenzyl alcohol to aldehydes, a reaction which exhibits double asymmetric induction.

Over the last ten years, we have developed titanium(salen) complex **1** as a highly effective catalyst for the asymmetric addition of a variety of cyanide sources to aldehydes, giving non-racemic cyanohydrin derivatives.[1] In particular, catalyst **1** has been shown to be compatible with trimethylsilyl cyanide,[2] ethyl cyanoformate,[3,4] acetyl cyanide,[4] and potassium cyanide.[3,5] Compared to other catalysts for asymmetric cyanohydrin synthesis,[6] complex **1** has the advantages of being active at high substrate to catalyst ratios (up to 1000 : 1) and at ambient temperature.[7]



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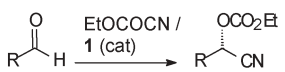
Of the various reactions catalysed by complex **1**, the asymmetric addition of ethyl cyanoformate to aldehydes (Scheme 1) is particularly attractive[8] in view of the low cost of the reagents, the 100% atom-economical nature of the reaction, the hydrolytic stability of cyanohydrin ethyl carbonates, and their significant synthetic potential; for example in palladium catalysed rearrangement processes.[9] However, under the conditions previously reported by both us[3] and others[4] for this transformation, 5 mol% of catalyst **1** is required to accomplish this transformation and this is not commercially viable. Therefore, we set out to develop reaction conditions under which this reaction could be achieved with high enantioselectivity, whilst using a lower amount of catalyst **1**. In this paper we report the achievement of this goal and its application to the synthesis of a variety of cyanohydrin carbonates.



Scheme 1 Asymmetric synthesis of cyanohydrin carbonates.

Since potassium cyanide is known to be a catalyst for the racemic synthesis of various cyanohydrin derivatives,[10] and catalyst **1** is known to be compatible with the presence of potassium cyanide,[5] we decided to investigate whether potassium cyanide (or an alternative cyanide source) could act as a cocatalyst in the asymmetric addition of cyanoformates to aldehydes catalysed by complex **1**.

Initial experiments were carried out in dichloromethane using benzaldehyde as the substrate, 1.2 equivalents of ethyl cyanoformate, and 1 mol% of catalyst **1**. Results of this study are shown in Table 1. As entry 1 shows, in the absence of potassium cyanide, the reaction was extremely slow under these conditions, even at room temperature. However, addition of just 1 mol% of solid potassium cyanide to the reaction resulted in a significant rate increase as shown in entry 2, and increasing the amount of potassium cyanide to 10 mol% resulted in a significant increase in the enantioselectivity (entry 3). To further enhance the enantioselectivity, the reaction temperature was reduced to −40 °C; the temperature previously found to be optimal in the absence of potassium cyanide.[3] As entry 4 shows, this did achieve the desired further increase in the enantioselectivity of the reaction, and by increasing the amount of catalyst **1** to 2 mol% (entry 5), the reaction could be driven to completion in one day and the same enantioselectivity could be obtained as that reported previously using 5 mol% of catalyst **1** and two equivalents of ethyl cyanoformate (entry 6).[3] Finally, the effect of further reducing the reaction temperature was investigated. However, as entry 7 shows, at −70 °C no reaction occurred under these conditions.

The optimal conditions for the addition of ethyl cyanoformate to aldehydes were taken as 24 hours at −40 °C, 1.2 equivalents of ethyl cyanoformate, 10 mol% of potassium cyanide and 1–2 mol% of catalyst **1**. Under these conditions, the asymmetric synthesis of six other cyanohydrin ethyl carbonates was investigated, with optimal results being presented in Table 2, alongside the enantioselectivities obtained under our previously reported conditions[3] for comparison. Electron rich and electron deficient aromatic aldehydes as well as α,β-unsaturated and aliphatic

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Table 1 Influence of potassium cyanide on the synthesis of mandelonitrile ethyl carbonate

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

[a] Result taken from reference 3 and using two equivalents of EtOCOCN. [b] ee values were determined by chiral GC.

Table 2 Potassium cyanide catalysed addition of ethyl cyanoformate to various aldehydes – RCHO

R	**1** (mol%)	Yield (%)	ee (%)[b]	Previous ee (%)[a]
4-$MeOC_6H_4$	2	98	97 (*S*)	95 (*S*)
4-$(CF_3)C_6H_4$	1	100	69 (*S*)	76 (*S*)
PhCH=CH	2	94	95 (*S*)	94 (*S*)
$CH_3(CH_2)_7$	2	90	79 (*S*)	84 (*S*)
Cy	1	86	74 (*S*)	79 (*S*)
Me_3C	2	79	68 (*S*)	76 (*S*)

[a] Results taken from reference 3. [b] ee values were determined by chiral GC and are accurate to ± 4%.

aldehydes were all found to be substrates under these conditions, and the enantioselectivities obtained by the two methods are comparable. *para*-Trifluoromethylbenzaldehyde is a particularly reactive substrate,[3] and its cyanohydrin ethyl carbonate was also found to racemise on standing. Either of these factors could explain the lower enantioselectivity obtained with this substrate. The low chemical yield and enantioselectivity observed with pivaldehyde and to a lesser extent with cyclohexane carboxaldehyde may be due to the sterically hindered nature of these substrates reducing the rate of the catalysed reaction under these reaction conditions. Two ketones (acetophenone and heptan-2-one) were also investigated as substrates, but no reaction occurred even at room temperature using 5 mol% of catalyst **1** and 10 mol% of potassium cyanide.

The influence of the structure of the cyanoformate on the reactivity and enantioselectivity of the reaction was investigated by comparing the use of methyl cyanoformate,[8,11] benzyl cyanoformate[8] and *tert*-butyl cyanoformate[12] with ethyl cyanoformate. These reactions were carried out using both benzaldehyde and pivaldehyde as substrates, and all were carried out using 2 mol% of catalyst **1**, 5 mol% of potassium cyanide and 1.2 equivalents of cyanoformate at −40 °C for 24 hours. Unfortunately, we were not able to find chromatography conditions under which either product obtained from benzyl cyanoformate, or the product obtained from benzaldehyde and *tert*-butyl cyanoformate could be separated. As shown in Table 3, where it could be determined, there was no significant change in the enantioselectivity between the various cyanoformates. Surprisingly however, the more sterically hindered cyanoformates (benzyl and *tert*-butyl) gave quantitative chemical yields with both benzaldehyde and pivaldehyde as substrate.

The compatibility of catalyst **1** with a wide range of cyanoformates allowed us to investigate a different approach to

Table 3 Influence of the cyanoformate

Substrate	Cyanoformate	Yield (%)	ee (%)[b]
PhCHO	MeOCOCN	92	95
PhCHO	EtOCOCN	100	95
PhCHO	BnOCOCN	100	[a]
PhCHO	$Me_3COCOCN$	100	[a]
Me_3CCHO	MeOCOCN	85	62
Me_3CCHO	EtOCOCN	79	68
Me_3CCHO	BnOCOCN	100	[a]
Me_3CCHO	$Me_3COCOCN$	100	65

[a] Could not be determined, but the product was optically active. [b] ee values were determined by chiral GC.

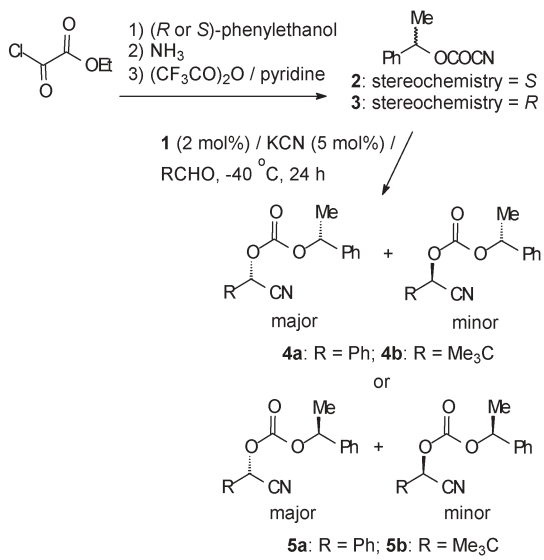
the synthesis of chiral cyanohydrin derivatives, namely diastereoselective cyanohydrin synthesis using a combination of catalyst **1** and a chiral cyanoformate. There are no previous reports of asymmetric cyanohydrin synthesis using chiral cyanide sources. Enantiomeric cyanoformates **2** and **3** derived from (*S*)- and (*R*)-1-phenylethanol respectively were synthesized by the route previously reported for *tert*-butyl cyanoformate[12] and outlined in Scheme 2. Reagents **2** and **3** were used in conjunction with (*R*,*R*)-**1** and 5 mol% of potassium cyanide to form the diastereomeric cyanohydrin carbonates **4a,b** and **5a,b** derived from benzaldehyde and pivaldehyde. Table 4 tabulates the diastereomeric ratios obtained for each of these reactions.

For both aldehydes, the major product obtained using cyanoformate **2** was shown by NMR spectroscopy to be diastereomeric with the major product obtained from cyanoformate **3**. This indicates that it is the stereochemistry of catalyst **1**

Table 4 Diastereoselective synthesis of cyanohydrin carbonates

Aldehyde	Cyanoformate	Yield (%)	Diastereomeric ratio[a]
PhCHO	**2**	66	18 : 1 (89% de)
PhCHO	**3**	71	28 : 1 (93% de)
Me_3CCHO	**2**	74	3.6 : 1 (57% de)
Me_3CCHO	**3**	97	5.3 : 1 (68% de)

[a] Diastereomeric ratios were determined by ^1H NMR spectroscopy.



Scheme 2 Diastereomeric synthesis of cyanohydrin carbonates.

rather than the stereochemistry of the cyanoformate that is primarily responsible for determining the configuration of the products. Since the (*R*,*R*)-enantiomer of catalyst **1** has been shown to always induce the formation of the (*S*)-enantiomer of a cyanohydrin for a wide range of substrates and cyanide sources, the major diastereomer of compounds **4–5a,b** is assumed to have the (*S*)-configuration at the newly created stereocentre. In both cases, a significantly higher diastereomeric ratio was observed using the combination of catalyst **1** and cyanoformate **3** than was obtained from catalyst **1** and cyanoformate **2**. Thus, the combination of **1** and **3** is a matched pair whilst **1** and **2** constitute a mismatched pair. The diastereomeric excesses obtained for the matched cases were almost identical to the enantiomeric excesses obtained using ethyl cyanoformate under the same conditions (*cf.* Table 1, entry 5 and the last entry in Table 2). Control experiments demonstrated that in the absence of potassium cyanide and/or catalyst **1**, no reaction occurred between benzaldehyde and cyanoformates **2/3**, even at room temperature.

All of the above reactions employing solid potassium cyanide as a cocatalyst for reactions conducted in dichloromethane were carried out under heterogeneous reaction conditions. We felt that if the reaction could be made homogeneous then it might be possible to further reduce the amount of catalyst **1** and/or decrease the reaction time. However, an initial reaction carried out at room temperature using tetrabutylammonium cyanide (5 mol%) in place of potassium cyanide along with catalyst **1** (2 mol%) and ethyl cyanoformate (1.2 equivalents) was not encouraging since although the reaction had gone to completion after 24 hours, mandelonitrile ethyl carbonate was obtained with just 4% ee.

The 1 : 1 complex **6** formed from potassium cyanide and 18-crown-6 is also known to be soluble in dichloromethane[13,14] and this reagent did allow the synthesis of cyanohydrin ethyl carbonates under homogeneous conditions. Thus, in the presence of just 1 mol% of complex **6** and 1.5 mol% of catalyst **1**, a wide range of aldehydes were converted into the corresponding cyanohydrin ethyl carbonates[3,9,15] in 24 hours at −40 °C as shown in Table 5. The results in Table 5 indicate that the enantioselectivities obtained using the potassium cyanide/18-crown-6 system are comparable with those obtained using 5 mol% of catalyst **1** or 2 mol% of catalyst **1** and 10 mol% of potassium cyanide.

Reactions carried out using less than 1.5 mol% of catalyst **1**, less than 1 mol% of complex **6**, or at temperatures below −40 °C failed to produce any mandelonitrile ethyl carbonate. Use of 3 mol% of complex **6** in combination with catalyst **1** (1.0 mol%) did give mandelonitrile ethyl carbonate, but with just 17% ee, presumably due to a facile uncatalysed reaction in the presence of higher concentrations of soluble cyanide.

In conclusion, we have shown that by use of potassium cyanide (either alone under heterogeneous conditions, or complexed to 18-crown-6 under homogeneous conditions) as a cocatalyst, the synthetic utility of the asymmetric addition of cyanoformates to aldehydes catalyzed by complex **1** can be increased. We have also demonstrated the first cases of diastereoselective cyanohydrin synthesis using chiral cyanoformates and shown that the stereochemistry of these reactions is principally controlled by catalyst **1** rather than the cyanoformate.

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Table 5 Potassium cyanide/18-crown-6 induced synthesis of cyanohydrin ethyl carbonates

R	Conversion (%)	ee (%)[b]	Previous ee (%)
Ph	100	91	95
2-MeC_6H_4	100	97	
4-MeC_6H_4	100	99	94
2-$MeOC_6H_4$	100	100	98
3-$MeOC_6H_4$	100	97	99
4-$MeOC_6H_4$	100	90	97
2-ClC_6H_4	100	93	
4-ClC_6H_4	100	100	94
PhCH=CH	100[a]	90	95
MeCH=CH	100	93	
EtCH=CH	100	91	
MeCH=C(Me)	100[a]	89	
$CH_3(CH_2)_7$	98	81	84
Cy	100	78	79
Me_3C	100	71	76

[a] Reaction required 48 hours to go to completion. [b] ee values were determined by chiral GC and are accurate to ± 4%.

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