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Catalytic, Asymmetric Synthesis of Cyanohydrin Ethyl Carbonates

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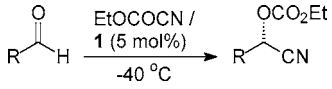
ABSTRACT



The bimetallic titanium complex [(salen)TiO]$_2$, where salen is the ligand derived from (*R*,*R*)-cyclohexanediamine and 3,5-di-*tert*-butyl-salicylaldehyde, has been shown to catalyze the asymmetric addition of ethyl cyanoformate to aldehydes leading to cyanohydrin carbonates with high enantiomeric excesses.

There is currently significant interest in asymmetric cyanohydrin synthesis due to the synthetic versatility of chiral cyanohydrins and their utility as chiral starting materials for natural product synthesis.[1] A range of catalyst classes are available for this reaction, including oxynitrilase enzymes, cyclic dipeptides, chiral Lewis bases, and chiral transition metal complexes. However, most of these methods require the use of either hydrogen cyanide or trimethylsilyl cyanide as the cyanide source. Both of these reagents are volatile and hence hazardous, and trimethylsilyl cyanide is also too expensive for commercial use. We have developed titanium complex **1** as a highly active catalyst for the addition of trimethylsilyl cyanide to both aldehydes[2] and ketones.[3] Recently, we have shown that complex **1** is also the only known catalyst that will accommodate potassium cyanide as the cyanide source in asymmetric cyanohydrin synthesis.[4]

Cyanoformate esters (ROCOCN) are known to react with aldehydes and ketones, leading directly to cyanohydrin carbonates.[5] Recently, asymmetric catalysts for this reaction have been reported. The first report in this area was by Tian and Deng in 2001, showing that dimeric chincona alkaloid derivatives would catalyze the asymmetric addition of ethyl cyanoformate to ketones, giving cyanohydrin ethyl carbonates with 59−97% enantiomeric excess.[6] This reaction, however, requires 10−30 mol % of the catalyst and reactions take up to 7 days. Subsequently, Shibasaki showed that a heterobimetallic complex derived from three binol units, three lithium ions, and a yttrium ion would catalyze the asymmetric addition of ethyl cyanoformate to aldehydes, producing non-racemic cyanohydrin carbonates.[7] Optimal results (87−98% enantiomeric excess) were obtained at −78 °C using

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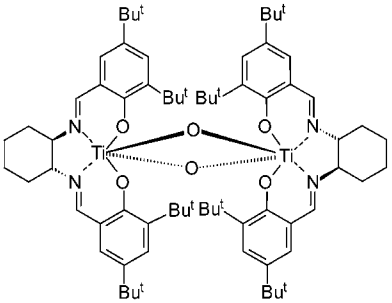
10 mol % of the catalyst and three additives: water (30 mol %), butyllithium (10 mol %), and tri(2,6-dimethoxyphenyl)phosphine oxide (10 mol %). Most recently, Nájera et al. have shown that an aluminum binol complex would catalyze the asymmetric addition of methyl cyanoformate to aldehydes at room temperature.[8] In this case, 10 mol % of the catalyst along with 4 Å molecular sieves were required to produce cyanohydrin carbonates with up to 80% enantiomeric excess.



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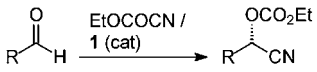
In view of this precedent, we decided to investigate the use of ethyl cyanoformate as a potential cyanide source for use in conjunction with catalyst **1** (Scheme 1). This would have the advantages of being less expensive than the use of trimethylsilyl cyanide, while avoiding the heterogeneous reaction conditions needed for reactions employing potassium cyanide and of being a completely atom-economical reaction. In addition, cyanohydrin carbonates are more stable toward unwanted hydrolysis than cyanohydrin trimethylsilyl ethers. In this communication, we present our results.

Scheme 1



For the initial study, benzaldehyde was selected as the substrate, and the addition of ethyl cyanoformate catalyzed by complex **1** was studied under various conditions as shown in Table 1. When 1 mol % of the catalyst was used at −85 °C in dichloromethane, no product was detected. However, raising the temperature to −73 °C resulted in complete reaction after 48 h to give (*S*)-mandelonitrile ethyl carbonate with a highly encouraging 94% enantiomeric excess.[9] Increasing the temperature further increased the rate of reaction but at the expense of a reduction in the enantiomeric excess of the product. Attempts to reduce the amount of catalyst to 0.1 mol % (the optimal amount for the addition of trimethylsilyl cyanide to benzaldehyde[2]) gave unsatisfactory results even at room temperature.

Table 1. Addition of Ethyl Cyanoformate to Benzaldehyde Catalyzed by Complex **1**

temp (°C)	**1** (mol %)	time (h)	completion (%)	ee (%)
−85	1	19	<3	
−73	1	48	100	94 (*S*)
−40	1	19	100	83 (*S*)
−40	0.1	72	<3	
25	0.1	148	<3	
−40	5	18	100	95 (*S*)
−40	10	51	100	93 (*S*)

While the result at −73 °C was encouraging, the long reaction time was felt to be impractical, so the effect of increasing the amount of catalyst was investigated to see if a similar enantiomeric excess could be obtained at a temperature where the rate of reaction was faster. Gratifyingly, use of 5 mol % of the catalyst at −40 °C resulted in the complete formation of (*S*)-mandelonitrile ethyl carbonate with 95% enantiomeric excess after just 18 h. This combination of catalyst mol %, reaction temperature, and product enantiomeric excess is a significant improvement on any of the previously known catalysts and was taken to be the optimal conditions for the use of complex **1**.

The addition of ethyl cyanoformate to other aldehydes was then investigated under these optimized conditions,[10] and the results are shown in Table 2. Electron-rich aromatic aldehydes were found to be excellent substrates for this reaction, giving cyanohydrin carbonates in high chemical yield and with excellent enantiomeric excesses. Thus, all three isomers of methoxybenzaldehyde and 4-methylbenzaldehyde gave products with 94−99% enantiomeric excess. Cinnamaldehyde was also found to be an excellent substrate giving a cyanohydrin carbonate with 94% enantiomeric excess. The introduction of an electron-withdrawing trifluoromethyl group onto the aromatic ring resulted in a very rapid reaction, albeit to give a product with a lower enantiomeric excess, possibly due to a competing uncatalyzed addition. 4-Chlorobenzaldehyde was, however, an excellent substrate, giving the corresponding cyanohydrin ethyl carbonate in high yield and with 94% enantiomeric excess. For all of these reactions with aromatic or α,*β*-unsaturated aldehydes, the use of 2 equiv of ethyl cyanoformate was necessary in order for the reactions to be complete in less than 20 h. The quantity of ethyl cyanoformate used could be reduced to just 1.2 equiv, though this resulted in extended reaction times of 45−68 h.

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(8) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197−200.

(9) All enantiomeric excesses were determined by chiral GLC and are accurate to ±3%.

(10) **Typical Experimental Procedure.** A stirred solution of benzaldehyde (0.48 mL, 4.7 mmol) in dichloromethane (20 mL) and (*R*)-**1** (5 mol %, 0.264 g, 0.22 mmol) was cooled to −84 °C, and EtOCOCN (0.93 mL, 9.4 mmol) was added in one portion. The yellow solution was then allowed to warm to −40 °C and then stirred vigorously for 19 h. To remove the catalyst, the filtrate was passed through a pad of silica eluting with dichloromethane. The solvent was removed in vacuo and the resulting orange-brown liquid dried in vacuo to give the crude cyanohydrin carbonate, which could be microdistilled to give mandelonitrile ethyl carbonate as a clear liquid (0.87 g, 90%): ee 95% (determined by chiral GC using a *γ*-CD butyryl, fused silica capillary column (30 m × 0.25 mm) with hydrogen as the carrier gas); $[\alpha]_D^{20}$ −20.1 (*c* 1.8 $CHCl_3$) [lit.[11] $[\alpha]^{20}_D$ +16.2 (*c* 2.8, $CHCl_3$) for (*R*)-enantiomer with 94% ee]; δ_H 1.26 (3H, t *J* 7.2), 4.21 (2H, q *J* 7.2), 6.19 (1H, s), 7.2−7.5 (5H, m).

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Table 2. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by Complex **1**

aldehyde	time (h)	EtOCOCN (equiv)	isolated yield (%)[a]	ee (%)
PhCHO	18	2	90	95
4-$MeOC_6H_4CHO$	18	2	92	95
3-$MeOC_6H_4CHO$	17	2	94	99
2-$MeOC_6H_4CHO$	48	1.2	95	98
4-MeC_6H_4CHO	48	1.2	67 (95)	94
4-$(CF_3)C_6H_4CHO$	6	2	84	76
4-ClC_6H_4CHO	68	1.2	96	94
PhCH=CHCHO	45	1.2	47 (99)	94
$C_8H_{17}CHO$	22	2	54	84
Me_2CHCHO	20	1.2	23 (88)	79
CyCHO	18	1.2	82	79
Me_3CCHO	48	1.2	69	76

[a] After purification by distillation. Number in brackets is the yield before distillation.

The aliphatic aldehydes studied all gave products with enantiomeric excesses of 76−84%. The primary aldehyde gave the product with the highest enantiomeric excess, but there was no significant difference between the enantioselectivity observed with the secondary and tertiary aldehydes. For the aliphatic aldehydes, the amount of ethyl cyanoformate used could be reduced to 1.2 equiv without the reaction time being extended beyond 20 h. The only exception was pivaldehyde which is a slow-reacting substrate, presumably for steric reasons.

In conclusion, we have shown that catalyst **1** will catalyze the asymmetric addition of ethyl cyanoformate to aldehydes, providing a very convenient synthesis of highly enantiomerically enriched cyanohydrin carbonates. Since both enantiomers of catalyst **1** are readily available, this methodology allows either enantiomer of the cyanohydrin carbonate to be prepared. Further work on the scope and mechanism of this reaction is in progress and will be reported in due course.

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