

Catalytic, Asymmetric Synthesis of Cyanohydrin Esters: The Effect of Anhydride Structure on Enantioselectivity

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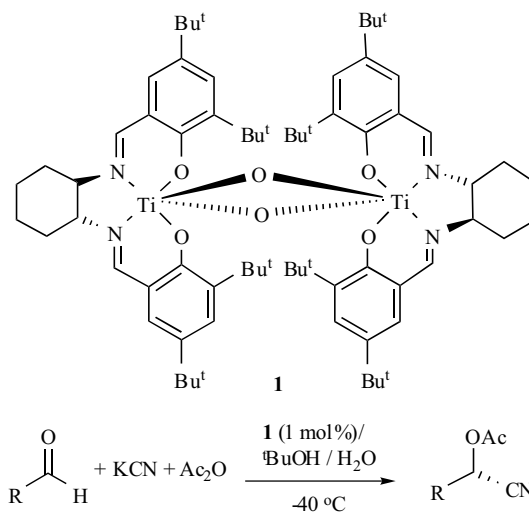
Abstract: A bimetallic titanium(salen) complex has been shown to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of a range of anhydrides, leading to cyanohydrin esters. Linear aliphatic anhydrides (acetic and propionic) gave products with higher enantiomeric purity than those obtained using pivalic or benzoic anhydrides.

Keywords: Cyanohydrin, catalyst, asymmetric, ester, titanium, salen.

In recent papers [1, 2] we have described the use of titanium complex **1** to catalyse the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes leading to non-racemic cyanohydrin acetates as shown in **Scheme 1**. This process is unique in that it is the only known process for the asymmetric, catalytic addition of cyanide to aldehydes, which utilises an inexpensive and non-volatile cyanide source. Other processes [3] require the use of hydrogen cyanide, trimethylsilyl cyanide or cyanofornate esters to accomplish similar transformations. Whilst the enantiomeric excesses of the cyanohydrin esters prepared using the chemistry shown in **Scheme 1** are respectable (60-93%), we were interested in enhancing these further. The only reagent in this process, which is amenable to systematic optimization is the anhydride, and in this communication we report on the effect that the structure of the anhydride has on the enantioselectivity of this process.

Initially, using benzaldehyde as the substrate and the standard conditions shown in **Scheme 1** [1, 2], the use of aliphatic anhydrides with different steric requirements, and the use of benzoic anhydride were investigated. The results are shown in **Table 1**. As can be seen, whilst propionic anhydride gave a product with comparable enantiomeric excess to that previously observed using acetic anhydride, pivalic anhydride and benzoic anhydride both gave products with significantly inferior enantiomeric excesses. Propionate esters of cyanohydrins are accessible by a number of routes [4], but the only previous asymmetric synthesis of these compounds involved an enzymatic resolution of the racemic ester or cyanohydrin [5]. Similarly, whilst a number of racemic synthesis of pivalate esters of cyanohydrins have been reported [6], only one synthesis of non-racemic cyanohydrin pivalates has been developed and this again involves an enzymatic resolution [7]. Benzoate esters of cyanohydrins are well known, with a number of asymmetric [8] and racemic [9] syntheses having been reported.

To investigate the generality of this trend in enantioselectivities, a range of aldehydes were studied using propionic anhydride for comparison with the results previously obtained using acetic anhydride [10]. Two other examples of reaction with pivalic anhydride were also investigated and the results are shown in **Table 2**. The data in **Table 2** show where a direct comparison between the anhydrides is possible, for aromatic aldehydes there is no significant difference between the use of acetic and propionic anhydride. However, for aliphatic aldehydes it is necessary to optimise the anhydride for each substrate. Thus, whilst acetic anhydride gives the higher enantioselectivity with isobutyraldehyde (72 versus 17%), propionic anhydride gives the better result with pivaldehyde (78 versus 62% enantiomeric excess). In all cases studied however, pivalic anhydride gave a product with a lower enantiomeric excess than either acetic or propionic anhydride. The enantiomeric excess of the product obtained from 4-trifluoromethylbenzaldehyde is also worthy of note as this product was found to undergo facile racemisation due to the acidity of its benzylic proton.



Scheme 1.

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Table 1. The Influence of Anhydride Structure on Enantioselectivity in the Synthesis of Mandelonitrile Esters

Anhydride	Enantiomeric excess of mandelonitrile ester ^a
Acetic anhydride	90 [1, 2]
Propionic anhydride	92
Pivalic anhydride	82
Benzoic anhydride	56

a) All enantiomeric excesses determined by chiral gas chromatography and are accurate to +/- 3%.

Table 2. Asymmetric Cyanohydrin Ester Formation^a

Aldehyde	Ee using acetic anhydride [1, 2]	Ee using propionic anhydride	Ee using pivalic anhydride
PhCHO	90	92	82
2-MeC ₆ H ₄ CHO		90	
3-MeC ₆ H ₄ CHO		95	
4-MeC ₆ H ₄ CHO		89	
3-MeOC ₆ H ₄ CHO	93	90	
4-MeOC ₆ H ₄ CHO	93	91	
4-ClC ₆ H ₄ CHO		90	
4-(CF ₃)C ₆ H ₄ CHO		82	62
PhCH=CHCHO		95	75
C ₈ H ₁₇ CHO		82	
CyCHO		41	
Me ₂ CHCHO	72	17	
Me ₃ CCHO	62	78	

a) All reactions were carried out using 1 mol% of catalyst **1** at -40 °C in dichloromethane. Reactions involving propionic or pivalic anhydride were 100% complete in 48 hours. For times / conversions using acetic anhydride see [1, 2].

In summary, we have shown that the enantioselective conversion of aldehydes into cyanohydrin esters catalysed by complex **1** can be optimised by judicious choice of the anhydride component of the reaction. Whilst the primary aliphatic anhydrides generally give comparable results for aromatic substrates, aliphatic aldehydes need to be optimised on a case to case basis. The less reactive anhydrides (pivalic and benzoic) give inferior results.

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- [10] Typical experimental procedure: To a stirred mixture of potassium cyanide (2.54 g, 39.2 mmol) and complex **1** (0.12 g,

0.098 mmol), in dichloromethane (30 mL) at -90 °C were added *tert*-butanol (0.98 mL), water (0.1 mL), aldehyde (9.8 mmol) and anhydride (39.2 mmol). The reaction was warmed to -40 °C and stirred for up to 48 hours until no aldehyde could be detected by GC. The reaction was then warmed to room temperature, filtered, and the solid washed with dichloromethane. The filtrate was passed through a pad of silica gel (10 mm x 50 mm) eluting with

dichloromethane to remove catalyst **1**. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography eluting with ethyl acetate / hexane to give the cyanohydrin ester. The enantiomeric excess of the products was determined by chiral GC using a γ -CD butyryl, fused silica capillary column (30m x 0.25 mm) with hydrogen as the carrier gas.