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Catalytic asymmetric synthesis of *O*-acetyl cyanohydrins from KCN, Ac_2O and aldehydes

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A (salen)titanium catalyst has been found to induce the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes, giving enantiomerically enriched cyanohydrin esters with up to 92% enantiomeric excess using just 1 mol% of the catalyst. This is the first report of the asymmetric synthesis of cyanohydrin derivatives using a cyanide source which is non-volatile and inexpensive.

Enantiomerically enriched cyanohydrins are versatile intermediates in organic synthesis, and many synthetic approaches to their syntheses are being pursued.[1] Catalytic ways of making this class of compounds rely on the asymmetric addition of a cyanide source to the carbonyl group of aldehydes, catalysed by enzymes[2] or synthetic chiral catalysts.[3] Enantiomerically enriched *O*-protected cyanohydrins are customarily made by the reaction of aldehydes with trimethylsilyl cyanide, usually catalysed by chiral Lewis acids.[1] We recently reported an efficient catalysis of this reaction based on a chiral binuclear Ti^{IV} salen complex **1a**,**b** which is active at a substrate : catalyst ratio as high as 1000 : 1 and promotes the addition at ambient temperatures with ee's in the range of 80–92%.[4] Very efficient catalysts based on bifunctional complexes of Al^{III} and Ti^{IV} have also been developed by Shibasaki's group, giving *O*-trimethylsilyl derivatives of cyanohydrins with ee's as high as 90–99% at −42 °C.[5]

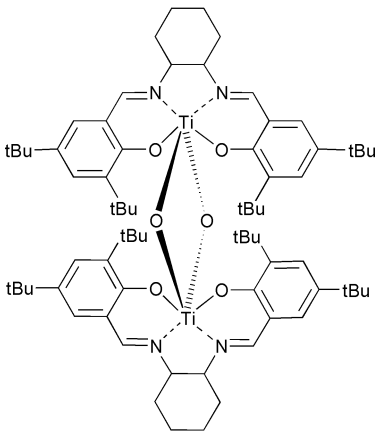
Unfortunately, trimethylsilyl cyanide is expensive and hydrogen cyanide is extremely toxic. Both of these reagents are also volatile. A method for the asymmetric synthesis of cyanohydrin derivatives from aldehydes which employs an inexpensive and non-volatile cyanide source would be highly advantageous. This paper reports the asymmetric synthesis of *O*-acetyl cyanohydrins by the reaction of potassium cyanide, acetic anhydride and aldehydes catalysed by complexes **1** (Scheme 1).[6]

Initial experiments revealed that the combination of potassium cyanide, benzaldehyde and acetic anhydride (added as the last ingredient) in the presence of 1 mol% of catalyst (**1a** or **1b**) did produce enantiomerically enriched *O*-acetyl cyanohydrins of (*S*)- or (*R*)-configuration respectively. The reaction showed good reproducibility and the absence of any side processes. The reaction was strongly dependent on the nature of the cyanide counter-ion. The best results for the model reaction, shown in Scheme 1, (dihydrocinnamaldehyde, alkali-metal cyanide, acetic anhydride, dichloromethane, −42 °C, 8 h under vigorous stirring in the presence of **1b**) were obtained by using potassium cyanide, and the range of enantiomeric purity of the resulting (*R*)-*O*-acetyl cyanohydrin was as follows: potassium cyanide (82% ee) > rubidium cyanide (76% ee) > sodium cyanide (56% ee) > caesium cyanide (54% ee) > lithium cyanide (4% ee). The addition of 1 equiv. of tetrabutylammonium bromide to the reaction mixture resulted in the formation of a completely racemic product.

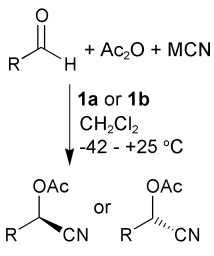
The reaction of benzaldehyde and potassium cyanide catalysed by **1a**, according to Scheme 1 was also solvent-dependent and at −25 °C after 8 h of stirring gave, (*S*)-*O*-acetyl mandelonitrile with the following ee's: 1,2-dichloroethane (90%) ≥ dichloromethane (88%) > toluene (78%) > tetrachloromethane (72%) > hexane (58%). The ee of the reaction was found to increase significantly from 73% at 20 °C to 89% at −25 °C, whilst a further decrease of the temperature to −42 °C did not produce any significant increase in the ee of the final product.

Fast and efficient stirring was very important in order to obtain good chemical yields during the reaction, but above a certain rotation speed (280 revolutions per minute), any further increase in the rate of stirring had no effect on the chemical yield. The curves shown in Fig. 1, describing the consumption of benzaldehyde at 20 °C in dichloromethane in the presence of potassium cyanide, acetic anhydride and **1b** or **1a** (1 mol%), were obtained in the stirring speed independent range and surprisingly testified to the first order kinetic behaviour of the reaction. Generally, without any additives the reaction was sluggish even at ambient temperatures, as the data of Fig. 1 illustrate (Fig. 1, curve 2).

Fortunately, some additives greatly accelerated the chemical reaction. We tested water, organic and mineral acids, nitrogen



1a stereochemistry = *R,R,R,R*
1b stereochemistry = *S,S,S,S*



R = Ar, alkyl; M = Li, Na, K, Rb, Cs

Scheme 1

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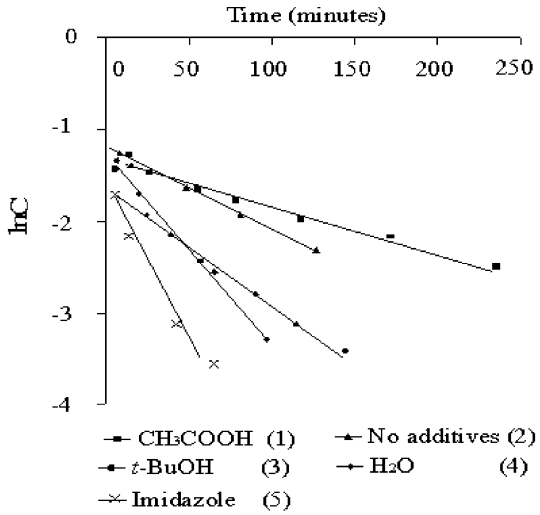

Fig. 1 First order kinetic plots at 20 °C.

bases, thiols, thiourea, carbon disufide, sodium tetraphenylborate, mineral carbonates, surfactants, phosphines and phosphine oxides for this purpose, but the most successful proved to be the use of imidazole (10 mol% relative to benzaldehyde), *tert*-butyl alcohol or water (100 mol% relative to benzaldehyde), as the data of Fig. 1 illustrate (Fig. 1, compare curves 1–5). The addition of acids generally and acetic acid in particular decreased the rate of the reaction (Fig. 1, curve 1) whereas replacement of potassium cyanide with hydrogen cyanide as well as addition of hydrogen cyanide (100 mol% with respect to potassium cyanide) to the reaction mixture led to a dramatic loss of optical purity (0% ee and 29% ee respectively). An attempt to use acetyl cyanide in place of the potassium cyanide–acetic anhydride failed, as no *O*-acetyl derivative of mandelonitrile was found in the reaction mixture under the standard reaction conditions.

The accelerating effects of water and *tert*-butyl alcohol were almost equal at rt (Fig. 1, curves 3 and 4) with both the reactions furnishing *O*-acetyl mandelonitrile in 90–91% chemical yield and 76–78% ee within 3 h. At a lower reaction temperature (−42 °C), *tert*-butyl alcohol became a more efficient (and reliable) additive, as compared with water although the ee of the reaction (90%) remained generally the same in both cases. The advantage of using *tert*-butyl alcohol became even more evident when conducting preparative experiments where chemical yields as high as 99% were obtained using this additive at −42 °C. Reactions have been carried out on up to a 200 g of aldehyde scale in a 2 L round bottomed flask without difficulty. With water as the additive the chemicals yields at −42 °C were disappointingly low.

Table 1 summarizes the results of asymmetric synthesis of different *O*-acetyl cyanohydrins, promoted by **1a** or **1b** under the optimal conditions found for the reaction using benzaldehyde as substrate. As can be seen from the data, aromatic aldehydes proved to be much better substrates than aliphatic aldehydes, and acetophenone was not a substrate for the reaction.

As HCN seems to be ruled out as a reagent in the reaction, the mechanism seems to be very similar to the one elaborated earlier for the asymmetric trimethylsilyl cyanation reaction of aldehydes promoted by **1a** or **1b**.[4] Notably, the ee's and sense of chirality of the cyanohydrin esters closely resemble the corresponding data for trimethylsilyl derivatives obtained with **1a** and **1b**.[4] The key feature of the mechanism is the formation of an intermediate chiral titanium–cyanide–metalloacetal complex where the cyanide ion attacks the aldehyde carbonyl carbon atom intramolecularly with the formation of a titanium-coordinated cyanohydrin. The breaking of the titanium–oxygen

Table 1 Enantioselective synthesis of *O*-acetyl cyanohydrins[a]

Aldehyde	Catalyst	Yield (%)[b]	Enantiomeric excess[c](%) (configuration)
PhCHO	**1a**	93	90 (*S*)
	1b	92[d]	89 (*R*)
p-$MeOC_6H_4CHO$	**1b**	74	93 (*R*)
m-$MeOC_6H_4CHO$	**1b**	99	93 (*R*)
m-$PhOC_6H_4CHO$	**1a**	99	90 (*S*)
	1b	99	89 (*R*)
p-FC_6H_4CHO	**1a**	98	92 (*S*)
	1b	99	93 (*R*)
o-FC_6H_4CHO	**1a**	87	85 (*S*)
	1b	86	82 (*R*)
m-FC_6H_4CHO	**1b**	99	89 (*R*)
o-ClC_6H_4CHO	**1a**	87	86 (*S*)
	1b	89[d]	88 (*R*)
$PhCH_2CH_2CHO$	**1a**	80	84 (*S*)
	1b	79[d]	82 (*R*)
Me_2CHCHO	**1a**	64	69 (*S*)
	1b	62[d]	72 (*R*)
Me_3CHO	**1a** (**1b**)	40	62 (*S*)
	1b	40[d]	60 (*R*)
PhCOMe	**1b**	No reaction	

[a] Reaction conditions: aldehyde (0.37–0.4 M), KCN, Ac_2O (mol ratio = 1:4:4), promoted by 1 mol% of **1b** (or **1a**) at −42°C, CH_2Cl_2, *t*-BuOH, stirring, 7 h.[b] Determined by NMR, adding an internal standard to the evaporated reaction mixture unless indicated otherwise.[c] Determined by chiral GLC.[d] Yield of isolated product.

bond by interaction with acetic anhydride or ROH may be the rate limiting step of the reaction. The latter feature of the mechanism can explain why imidazole, water and *tert*-butyl alcohol catalyse the reaction. The free cyanohydrins formed in this way undergo easy acylation without racemization, as control experiments indicated.

Mechanistic investigations of the process as well as further attempts to increase both optical and chemical yields (especially for aliphatic aldehydes) are still in progress and will be reported in due course. In summary, we have developed a very efficient procedure to prepare enantiomerically enriched *O*-protected cyanohydrins with very good chemical yields and ee's, starting with inexpensive and non-volatile starting materials.

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6 This work has been patented: patent application number 0018973.8.