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Lewis Acid–Lewis Base-Catalysed Enantioselective Addition of α-Ketonitriles to Aldehydes

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Abstract: Additions of structurally diverse α-ketonitriles to aromatic and aliphatic prochiral aldehydes yielding highly enantioenriched acylated cyanohydrins were achieved using a combination of a titanium salen dimer and an achiral or chiral Lewis base. In most cases high yields and high enantioselectivities were observed. The *ee* was moderate in the initial part of the reaction but increased over time. This could be avoided, and higher *ee*s obtained, by keeping the titanium complex, in the presence or absence of aldehyde and ketonitrile, at −40 °C prior to the addition of the Lewis base. A mechanism initiated by nucleophilic attack of the tertiary amine at the carbonyl carbon atom of the ketonitile is supported by ^{13}C labelling experiments.

Keywords: *O*-acylcyanohydrins; Lewis acids; Lewis bases; salen; titanium

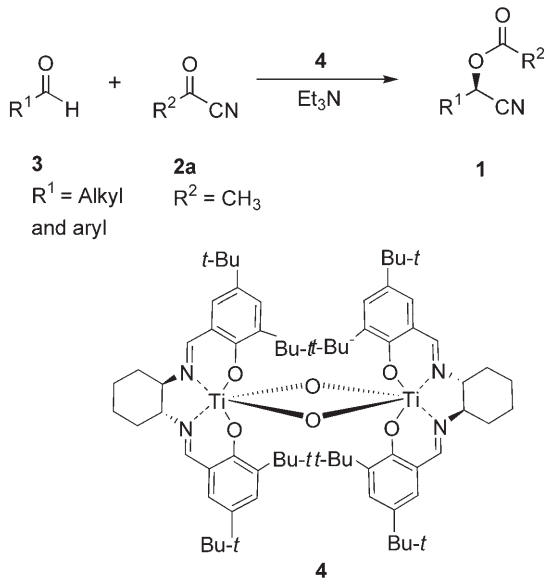
Introduction

Chiral enantiomerically pure cyanohydrins serve as versatile synthetic building blocks, and enantioselective cyanantions of prochiral carbonyl compounds are therefore currently being extensively studied.[1] Procedures allowing direct access to *O*-protected non-racemic cyanohydrins are essential in order to avoid reversibility of the cyanide addition, which may lead to decreasing enantioselectivity. Several procedures affording *O*-silylated,[2] *O*-phosphorylated,[3] and *O*-formylated[4] products from both aldehydes and ketones are now well established. Acylated cyanohydrins (**1**) constitute other important synthetic intermediates, which can undergo further transformations without loss of enantiomeric purity.[5] They are also in themselves important synthetic targets, which have found commercial applications as potent insecticides.[6]

Enantioenriched acylated cyanohydrins have been obtained *via* several indirect methods. Esterification without stereochemical deterioration of non-racemic preformed *O*-trimethylsilylated cyanohydrins was achieved using acid chlorides or anhydrides in the presence of catalytic amounts of $Sc(OTf)_3$.[7] A more convenient one-pot procedure which, however, required large excess of reagents, was described, whereby enantioselective cyanation of aldehydes using KCN was performed in the presence of acetic anhydride.[8] Another one-pot procedure based on dynamic kinetic resolution of *in situ* obtained racemic cyanohydrins using lipase B from *Candida antarctica* in the presence of an acylating agent, led to slow formation of enantioenriched cyanohydrin esters.[9]

Procedures for direct additions of α-ketonitriles to prochiral aldehydes, avoiding the formation of accompanying products, are attractive due to their simplicity and atom economy. This has been achieved in several non-selective processes yielding racemic products. Thus, addition of benzoyl cyanide to benzaldehyde in the presence of catalytic amounts of potassium hydroxide was shown already in 1949 to afford the benzoate of the cyanohydrin,[10] and later aqueous acetonitrile together with potassium carbonate[11] and even DMSO without any base[12] were employed for the same purpose. Tributyltin cyanide was also shown to catalyse the addition of acetyl cyanide to several aldehydes.[13] More general conditions, allowing the preparation of cyanohydrin esters from a variety of aldehydes and keto esters, were found using DABCO[14] or DBU[15] as a Lewis base catalyst.

We were recently able to demonstrate that, using a safe and convenient catalytic system capable of a dual Lewis acid-Lewis base activation,[16] highly enantioenriched acetylated cyanohydrins (**1**) were formed in high yields from acetyl cyanide (**2a**) and aromatic as well as aliphatic aldehydes (**3**, Scheme 1).[17] Our work was followed by the first enantioselective cyanobenzoylation, reported by Sansano, Najera, and co-workers.[18] We also developed an enzymatic method for the rapid determination of conversion of starting material and enantiomeric excess of the product.[19] Direct access to other *O*-acylated cyanohydrins is of



Scheme 1.

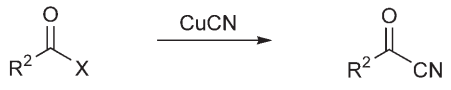
interest due to their usefulness as both synthetic targets and intermediates. We have now extended the scope of the catalytic reaction to include a further variety of combinations of aldehydes and α-ketonitriles and performed experiments which cast light on the mechanism of the reaction.

Results and Discussion

Preparation of α-Ketonitriles

α-Ketonitriles[20] were first described as early as 1832 when Wöhler and Liebig prepared benzoyl cyanide from benzoyl chloride and HgCN.[21] Other metal salts, such as AgCN[22] and Bu_3SnCN,[23] HCN in combination with pyridine,[24] phase-transfer catalysis,[25] Me_3SiCN,[26] and KCN together with ZnI_2 and PEG400[27] have later been used in place of HgCN together with acid chlorides or bromides. Acetyl cyanide was prepared from acetyl bromide and CuCN in 1944,[28] but due to the propensity of enolisable acyl cyanides to be converted to their acylated enols in the presence of base, satisfactory and more general methods for the preparation of aliphatic acyl cyanides appeared only later.[20] Normant found that high yields of aliphatic as well as aromatic ketonitriles were obtained from acid chlorides and CuCN in the presence of LiI or using acetonitrile as solvent.[29]

We prepared α-ketonitriles **2b–g** by reacting acyl chlorides or bromides with CuCN (Scheme 2). We found heterogenous conditions, without solvent, to be optimal for low-boiling products which could be distilled directly from the reaction mixture, whereas acetonitrile was used as solvent for less volatile products. These methods offer a facile synthesis of ketonitriles from primary, secondary and tertiary alkyl and olefinic acid halides. No by-products, such as acyl cyanide dimers, were observed.



2b X = Br, $R^2 = CH_2CH_3$, 74%
2c X = Br, $R^2 = (CH_2)_2CH_3$, 71%
2d X = Br, $R^2 = (CH_2)_3CH_3$, 75 %
2e X = Br, $R^2 = CH(CH_3)_2$, 79%
2f X = Br, $R^2 = C(CH_3)_3$, 68%
2g X = Cl, R^2 = (*E*)-CH=CHPh, 81%

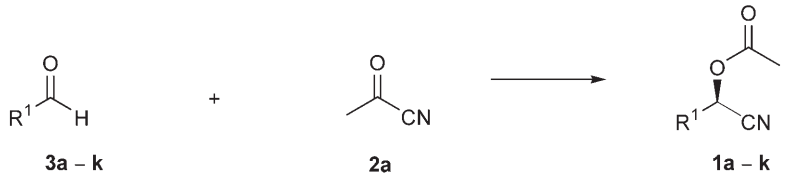
Scheme 2.

Asymmetric Synthesis of Cyanohydrin Esters

Our previously reported conditions for the synthesis of a variety of cyanohydrin esters from different aldehydes and acetyl cyanide used a combination of Ti-salen dimer (**4**) and triethylamine. These conditions were applicable to a large varity of combinations of aldehydes and ketonitriles (Table 1). Good yields (72–93%) and enantioselectivities (85–96% *ee*) were achieved using aromatic aldehydes and acetyl cyanide (entries 1–8), the only exception being 2-pyridinecarboxaldehyde, which gave lower enantioselectivity (20% *ee*, entry 8). The position of the aldehyde substituent thus seems to be crucial for the selectivity since 3-pyridinecarboxaldehyde gave significantly higher *ee* (86%, entry 7). *m*-Phenoxybenzaldehyde was less reactive and required longer reaction time (48 h instead of 8–12 h) probably because of steric hindrance by the phenoxy group (entry 6). Unsaturated and aliphatic aldehydes gave high enantiomeric excesses and isolated yields (entries 9–11).

Benzaldehyde was selected for reactions with ketonitriles **2b–h** (Table 2). The reactivity was shown to be influenced by the structure of the ketonitrile and decreased with increased size of the alkyl group. Linear aliphatic ketonitriles reacted smoothly to afford high yields (85–90%) of highly enantioenriched (92–93% *ee*) products (entries 1–4). While 3-methyl-2-oxobutanenitrile **2e** exhibited equally high reactivity as the linear compounds (entry 5), 3,3-dimethyl-2-oxobutanenitrile **(2f)** was unreactive at −40 °C. Increasing the temperature to room temperature gave a product with 79% *ee* in 81% isolated yield (entry 6). Cinnamoyl cyanide (**2g**) was the most reactive ketonitrile and gave the acetylated product in high isolated yield with excellent *ee* after only four hours (entry 7). Benzoyl cyanide (**2h**) provided the product with high isolated yield and good *ee* (76% yield and 75% *ee*

Table 1. Cyanation of aldehydes by acetyl cyanide (**2a**).[a]



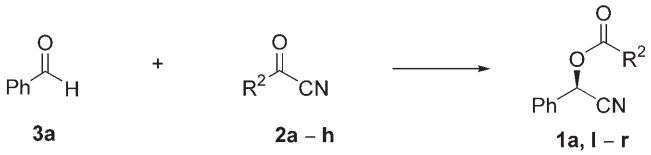
3a – k **2a** **1a – k**

1a $R^1 = C_6H_5$ **1e** R^1 = 2-Furyl **1i** R^1 = (*E*)-CH=CHPh
1b R^1 = 4-CH_3-C_6H_4 **1f** R^1 = 3-(PhO)C_6H_4 **1j** $R^1 = C(CH_3)_3$
1c R^1 = 4-CH_3O-C_6H_4 **1g** R^1 = 3-Pyridyl **1k** $R^1 = (CH_2)_4CH_3$
1d R^1 = 4-Cl-C_6H_4 **1h** R^1 = 2-Pyridyl

Entry	Aldehyde [R^1]	Product	Time (h)	Yield [%][b]	*ee* [%][c] (abs. conf.)[d]
1[17]	**3a** [C_6H_5]	**1a**	10	89	94 (*S*)
2[17]	**3b** [4-CH_3-C_6H_4]	**1b**	10	90	96 (*S*)
3[17]	**3c** [4-CH_3O-C_6H_4]	**1c**	12	72	94(*S*)
4[17]	**3d** [4-Cl-C_6H_4]	**1d**	8	89	95 (*S*)
5	**3e** [2-furyl]	**1e**	12	93	89 (*R*)
6	**3f** [3-PhO-C_6H_4]	**1f**	48	84	85 (*S*)
7	**3g** [3-Pyridyl]	**1g**	12	91	86 (n.d.)
8	**3h** [2-Pyridyl]	**1h**	12	87	20 (n.d.)
9[17]	**3i** [(*E*)-CH=CHPh]	**1i**	12	64	93 (*S*)
10[17]	**3j** [$C(CH_3)_3$]	**1j**	6	84	76 (*S*)
11[17]	**3k** [$(CH_2)_4CH_3$]	**1k**	6	89	90 (*S*)

[a] Reactions were carried out in dichloromethane at −40 °C using 1 equiv. of aldehyde, 2 equivs. of ketonitrile, 5 mol % **4** and 10 mol % Et_3N.
[b] Isolated yield.
[c] Determined by chiral GC or chiral HPLC.
[d] Assigned by comparison with literature value.

Table 2. Cyanation of benzaldehyde by α-ketonitriles.[a]



3a **2a – h** **1a, l – r**

1a $R^2 = CH_3$ **1o** $R^2 = CH(CH_3)_2$
1l $R^2 = CH_2CH_3$ **1p** $R^2 = C(CH_3)_3$
1m $R^2 = (CH_2)_2CH_3$ **1q** R^2 = (*E*)-CH=CHPh
1n $R^2 = (CH_2)_3CH_3$ **1r** $R^2 = C_6H_5$

Entry	α-Ketonitrile [R^2]	Product	Time [h]	Yield [%][b]	*ee* [%][c] (abs. conf.)[d]
1[17]	**2a** [CH_3]	**1a**	10	89	94 (*S*)
2	**2b** [CH_2CH_3]	**1l**	10	89	93 (*S*)
3	**2c** [$(CH_2)_2CH_3$]	**1m**	10	90	92 (*S*)
4	**2d** [$(CH_2)_3CH_3$]	**1n**	10	85	93 (*S*)
5	**2e** [$CH(CH_3)_2$]	**1o**	10	86	92 (*S*)
6[e]	**2f** [$C(CH_3)_3$]	**1p**	10	81	79 (*S*)
7	**2g** [(*E*)-CH=CHPh]	**1q**	4	89	94 (*S*)
8	**2h** [C_6H_5]	**1r**	26	76	75 (*S*)

[a] Reactions were carried out in dichloromethane at −40 °C using 1 equiv. of aldehyde, 2 equivs. of ketonitrile, 5 mol % **4** and 10 mol % Et_3N.
[b] Isolated yield.
[c] Determined by chiral GC or chiral HPLC.
[d] Assigned by comparison with literature value.
[e] The reaction was carried out at room temperature.

(entry 8), as compared to 68% *ee* using the catalytic system of Sansano, Najera, and co-workers[18]).

Influence of the Lewis Base

The Ti dimer **4** did not catalyse the addition of ketonitriles to benzaldehyde at −40 °C in the absence of a Lewis base (Table 3, entry 1). Best results for the addition of acetyl cyanide were obtained with triethylamine (entry 2). While a range of other tertiary Lewis bases afforded acceptable results (entries 3–5), a secondary amine provided a catalytic system with inferior properties (entry 6). DBU exhibited high reactivity, but at the expense of the enantioselectivity (entry 7, *vide infra*). In contrast to DMAP, pyridine did not catalyse the reaction (entry 8). Chiral bases influenced the enantioselectivity only to a minor extent, as seen from results using **4** and *ent*-**4** (entries 9 and 10).

Results similar to those obtained using acetyl cyanide were obtained from reactions with 2-oxobutanenitrile (**2b**, entries 11–14) whereas 3,3-dimethyl-2-oxobutanenitrile (**2f**) exhibited lower reactivity and/or selectivity (entries 15–18). As expected, higher reactivity and reasonable selectivity were observed at room temperature, except for DBU which under all conditions gave reactions with low selectivity (entries 19–21).

Mechanistic Aspects

The proximity of the CO and CN groups in α-ketonitriles enhances the electrophilicity of both functions. Propionyl cyanide was already in 1880 shown to yield a dimer in the presence of cyanide ions.[30] The dimerisation was shown to occur by initial attack of cyanide on the carbonyl group, followed by acetylation of the alcoholate.[31] Although nucleophiles as a rule add to the carbonyl group of ketonitriles,[32] attack at the nitrile carbon atom by soft nucleophiles such as H_2S[33] and azides[34] has been observed. Whereas strongly basic nucleophiles like diethylamine and piperidine were shown to react instantaneously with acetyl cyanide at 245 K to yield an amide and hydrogen cyanide, tetrahedral intermediates were observed by ^{13}C NMR spectroscopy from a variety of more weakly basic nucleophiles.[35]

Acetyl cyanide has also been employed for the acetylation of alcohols. In the presence of DMAP an active acylating agent was obtained. The counterion affected the rate and selectivity, as shown by a com-

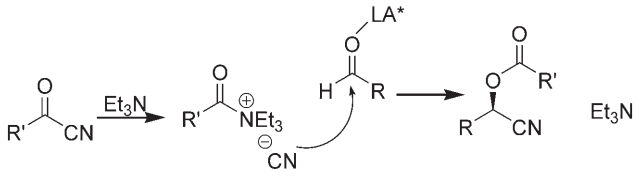
Table 3. Influence of different bases on the cyanation of benzaldehyde by α-ketonitriles.[a]

Entry	Lewis base	α-Ketonitrile [R^2]	Time [h]	Conv. [%][b]	*ee* [%][c] (abs. conf.)[d]
1[17]	-	**2a** [CH_3]	24	0	-
2[17]	Et_3N	**2a** [CH_3]	8	96	94 (*S*)
3[17]	DMAP	**2a** [CH_3]	6	57	94 (*S*)
4[17]	DABCO	**2a** [CH_3]	9	67	92 (*S*)
5[17]	DIEA	**2a** [CH_3]	8	97	81 (*S*)
6	Diethylamine	**2a** [CH_3]	8	41	81 (*S*)
7	DBU	**2a** [CH_3]	2	99	20 (*S*)
8	Pyridine	**2a** [CH_3]	24	0	-
9[17]	Cinchonidine	**2a** [CH_3]	9	78	96 (*S*)
10[17],[e]	Cinchonidine	**2a** [CH_3]	9	75	92 (*R*)
11	Et_3N	**2b** [CH_2CH_3]	10	94	93 (*S*)
12	DABCO	**2b** [CH_2CH_3]	9	53	92 (*S*)
13	DBU	**2b** [CH_2CH_3]	0.5	99	12 (*S*)
14	DIEA	**2b** [CH_2CH_3]	8	98	78 (*S*)
15	Et_3N	**2f** [$C(CH_3)_3$]	24	0	-
16	DABCO	**2f** [$C(CH_3)_3$]	24	0	-
17	DBU	**2f** [$C(CH_3)_3$]	5	62	0
18	DIEA	**2f** [$C(CH_3)_3$]	24	0	-
19[f]	DABCO	**2f** [$C(CH_3)_3$]	4	49	79 (*S*)
20[f]	DBU	**2f** [$C(CH_3)_3$]	4	100	6 (*S*)
21[f]	DIEA	**2f** [$C(CH_3)_3$]	4	56	76 (*S*)

[a] Reactions were carried out in dichloromethane at −40 °C using 1 equiv. of aldehyde, 2 equivs. of ketonitrile, 5 mol% **4** and 10 mol% Lewis base.
[b] Determined by GC/MS.
[c] Determined by chiral GC.
[d] Assigned by comparison with literature value.
[e] *ent*-**4** was used.
[f] The reaction was carried out at room temperature.

parison with reagents obtained from acetyl cyanide, acetyl chloride and acetic anhydride.[36] Selective acetylation of a primary alcohol in the presence of a secondary alcohol was recently achieved employing acetyl cyanide and triethylamine.[37]

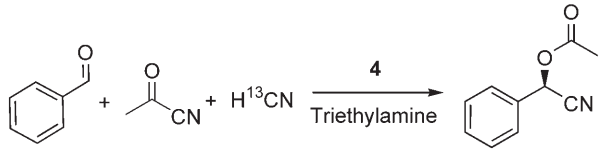
On the basis of the known reactivity of ketonitriles, it seems reasonable that the first step in the catalytic reaction is the attack of the Lewis base on the carbonyl group of the acyl cyanide with formation of cyanide ion and a potent acylating agent, which both can react with the aldehyde to form the observed product (Scheme 3). This mechanism has previously been sug-



Scheme 3.

gested for cyanoacylations in the presence of DABCO[14] and recently also DBU,[15] which indeed can serve as a potent nucleophile.[38]

An alternative mechanism was proposed for cyanobenzoylation of aldehydes.[18] It was suggested that the reaction is initiated by cyanide ions obtained by deprotonation of the small amount of HCN present in the ketonitrile. However, knowing that amines readily attack the carbonyl function of α-ketonitriles and that a superior acylating agent thereby is obtained, we favour the route proposed above. In addition, deprotonation is highly inefficient in dichloromethane; the ^{1}H NMR spectrum of a mixture of HCN and triethylamine in CD_2Cl_2 shows no trietylammonium ion. This fact is, however, no strict proof against the suggested mechanism, as a low concentration of cyanide may be sufficient to initiate the process. Therefore, in order to further study the possibility that the reaction is initiated by HCN, two equivalents of ^{13}C-labeled HCN were bubbled through the reaction solution before addition of the reactants (Scheme 4). A mass spectrum recorded after 5% conversion showed no ^{13}C incorporation in the product, demonstrating that HCN does not serve as a source of cyanide ion. This experiment also shows that free cyanide is probably not present



Scheme 4.

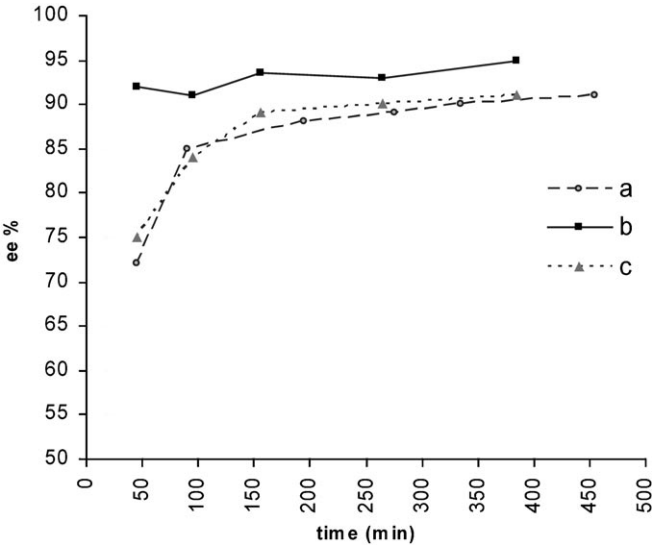


Figure 1. a) Normal conditions, b) Ti-salen complex kept at −40 °C for 3 h before the addition of aldehyde, ketonitrile, and Lewis base, c) Ti-salen complex kept at room temperature for 3 h before cooling to −40 °C and addition of aldehyde, ketonitrile, and Lewis base.

in the solution, as that would lead to ^{13}C exchange between H^{13}CN and CN$^-$.

It has previously been observed that, in cyanations using the Ti-salen dimer **4**, the enantioselectivity increases with time.[39] The same phenomenon was observed in the present cyanations. Thus, the addition of aldehyde and acetyl cyanide to dimer **4** and triethylamine resulted in immediate product formation. After 45 min, merely 70% *ee* was observed, whereas the final *ee* was 91% (Figure 1). However, when the reaction mixture was kept at −40 °C for 3 h in the absence of Lewis base, no product was formed. Upon subsequent addition of Lewis base, the reaction started, giving product with a constant and somewhat higher *ee* value than that observed under normal conditions (95%). The same result was obtained when only the Ti-salen complex was kept at −40 °C for 3 h before the addition of aldehyde, ketonitrile, and Lewis base (Figure 1). When the reaction mixture was stirred at room temperature for 3 h prior to cooling to −40 °C and the aldehyde, ketonitrile, and Lewis base added at that temperature, the *ee* was again lower in the initial part of the reaction and increased with time.

In order to gain some information about this effect, ^{1}H NMR spectra of the Ti complex were recorded at intervals at −40 °C. At room temperature the dimer to monomer ratio was 4:1 as shown by the integration of the aromatic protons [$\delta = 7.55$ ppm (s, 1H, ArH) for the monomer and $\delta = 7.41$ ppm (s, 1H, ArH) for the dimer]. Spectra taken immediately after cooling the solution showed a ratio of dimer to monomer of 90:10. This increased over time and was found to be 95:5 after 90 min and then constant. No other change

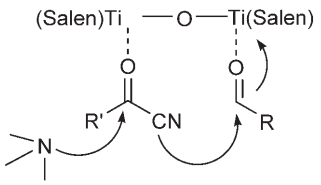


Figure 2. Proposed mechanism for addition of ketonitriles to aldehydes.

in the spectrum was observed. Heating the sample to room temperature restored the original 4:1 ratio.[40]

It thus seems as if high *ee* values are obtained in reactions catalysed by the dimeric Ti complex. Belokon′, North and co-workers used two different aldehydes in order to study the variation of *ee*.[39] A sacrificial aldehyde was assumed to convert the precatalyst to the catalytically active species. Using this species in the reaction of the second aldehyde afforded the product with an *ee* which was constant over time, but somewhat lower than that observed under normal conditions.

Deterioration of *ee*, seemingly caused by the presence of the Ti-salen monomer, was expected to be most serious for highly reactive systems, since a large part of the catalytic reaction occurs before the monomer to dimer equilibrium is established. In order to test this assumption, the reaction of benzaldehyde with acetyl cyanide using DBU as the Lewis base was run at −40 °C and the reactants stirred at this temperature for 3 h before addition of the base. This procedure did indeed result in a product with higher *ee*, 69 % as compared to 20 % under normal conditions.

Considering the results reported here, it seems reasonable that the two carbonyl species, the aldehyde and the ketonitrile, are coordinated to the two Ti atoms of the dimeric Ti-salen complex. The ^{13}C NMR signal from the carbonyl carbon atom of acetyl cyanide was indeed found to be shifted in the presence of the Ti complex, corroborating this assumption. Cyanide delivery within the catalytic complex would explain the lack of isotope scrambling between labelled cyanide from the ketonitrile and non-labelled HCN (Figure 2).

Conclusions

An efficient catalytic system consisting of a chiral Lewis acid and an achiral or chiral Lewis base was found for the 100 % atom economic addition of ketonitriles to aldehydes affording highly enantioenriched synthetically important *O*-acylated cyanohydrins in high yields. Experimental data support a mechanism involving attack of the Lewis base on the carbonyl carbon atom of the ketonitrile coordinated to Ti, thereby providing the cyanide and acylated ammonium compound required for reaction with the Lewis acid activated aldehyde.

Experimental Section

General Remarks

Benzaldehyde, CH_2Cl_2 and Et_3N were distilled over CaH_2. All bases were distilled before use. Aldehydes, pyruvonitrile and benzoyl cyanide were purchased from Aldrich, stored under N_2, and used without further purification. The Ti-salen catalyst (**4**) was prepared by following the published procedure.[2a,8b] All reactions were performed under N_2. Conversions were determined by GC/MS and the enantiomeric excesses by GC analysis using a chiral column [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm] or by HPLC using a chiral column (Daicel Chiralcel OD-H, 0.46 cm Ø × 25 cm). ^{1}H NMR spectra were recorded at 500 or 400 MHz, ^{13}C spectra at 125 or 100 MHz. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to the solvent as internal standard.

General Procedure for Synthesis of Liquid α-Ketonitriles (2b–f)[41]

The acid bromide (22 mmol) was added to CuCN (26.6 mmol, 1.2 equivs.) under N_2 and the heterogeneous mixture was stirred for 2 h at 90 °C before distilled to yield the α-ketonitrile.

2-Oxobutanenitrile (2b): Yield: 74 %; ^{1}H NMR ($CDCl_3$): $\delta = 0.79$ (q, $\delta = 7.3$ Hz, 2H, CH_2), 1.24 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 177.4$, 113.2, 38.8, 6.8; MS (EI): $m/z := 83.0$ [M^+]. Other spectral data were in accordance with those previously published.[26b]

2-Oxopentanenitrile (2c): Yield: 71 %; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.72$ (t, $J = 7.3$ Hz, 2H, CH_2), 1.78 (tq, 7.3 Hz, 2H, CH_2), 1.00 (t, $J = 7.3$, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 176.9$, 113.3, 46.8, 16.4, 13.1; MS (EI): $m/z =$ 97.10 [M^+]. Other spectral data were in accordance with those previously published.[26b,29]

2-Oxohexanenitrile (2d): Yield: 75 %; ^{1}H NMR ($CDCl_3$): $\delta = 2.74$ (t, $J = 7.6$ Hz, 2H, CH_2), 1.69–1.76 (tt, $J = 7.6$ Hz, 2H, CH_2), 1.34–1.44 (tq, $J = 7.6$ Hz, 2H, CH_2), 0.95 (t, $J =$ 7.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 177.1$, 113.3, 44.8, 24.8, 21.8, 13.6; MS (EI): $m/z = 111.10$ [M^+]. Other spectral data were in accordance with those previously published.[29]

3-Methyl-2-oxobutanenitrile (2e): Yield: 79 %; ^{1}H NMR ($CDCl_3$): $\delta = 2.79$ (hept, $J = 6.9$ Hz, 2H), 1.30 (d, $J = 6.9$ Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 181.1$, 112.9, 43.1, 16.7 ppm; MS (EI): $m/z = 97.05$ [M^+]. Other spectral data were in accordance with those previously published.[42]

3,3-Dimethyl-2-oxobutanenitrile (2f): Yield: 63 %; ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 183.1$, 112.1, 45.0, 24.5; MS (EI): $m/z = 111.10$ [M^+]. Other spectral data were in accordance with those previously published.[26b]

(3*E*)-2-Oxo-4-phenylbutenenitrile (2g)[29]

A solution of *trans*-cinnamic acid (1.0 g, 6.7 mmol), oxalyl chloride (0.71 mL, 8.1 mmol) and DMF (10 μL, 0.13 mmol)

in CH_2Cl_2 (40 mL) was refluxed for 2 h under N_2. The solvent was removed under vacuum and CuCN (1.2 g, 13.5 mmol) was added followed by dry acetonitrile (6 mL). The suspension was refluxed for 40 min under N_2 and the resulting clear solution was cooled to ambient temperature before the solvent was removed under vacuum. Dry Et_2O (100 mL) was added and the mixture was heated to reflux and filtered under N_2 while still hot. The solvent was removed from the filtrate to give the product; yield: 81%; ^{1}H NMR ($CDCl_3$): $\delta = 8.01$ (d, $J = 16.1$ Hz, 1H, CH), 7.65 (m, 2H, Ph), 7.55 (m, 1H, Ph), 7.49 (m, 2H, Ph), 6.87 (d, $J = 16.1$ Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): $\delta = 167.5$, 155.0, 133,1, 132.8, 129.5, 129.4, 125,3, 112.4; MS (EI): $m/z = 157.0$ [M^+]. Spectral data were in accordance with those previously published.[43]

General Procedure for Enantioselective Addition of α-Ketonitrile to Aldehydes

Aldehyde (1 equiv.) was added to a solution of **4** (132 mg, 5 mol%) and base (10 mol%) in dichloromethane (10 mL). The solution was cooled to −40 °C before α-ketonitrile (2 equivs.) was added in one portion and the reaction was monitored with GC/MS. After dilution with Et_2O, the reaction mixture was filtered through silica and the solvent was evaporated under vacuum. The residue was purified by distillation or by column chromatography to give the pure product.

***O*-Acetyl-(*R*)-2-hydroxy-(2-furyl)acetonitrile (1e):** Chiral GC, pressure 23 psi; injection temp. 225 °C; initial column temp. 110 °C; detection temp. 225 °C; retention time (t_R) of 8.3 min (minor), 22.2 min (major). Spectral data were in accordance with those previously published.[9] The absolute configuration was determined from the sign of optical rotation.[9]

***O*-Acetyl-(*S*)-2-hydroxy-2-(3-phenoxyphenyl)acetonitrile (1f):** Chiral HPLC, 2-propanol/hexane, 1/9. Flow: 0.8 mL min^{-1}; detection 212 nm; retention time (t_R) of 15.1 min (major), 19.4 min (minor). Spectral data were in accordance with those previously published.[44] The absolute configuration was determined from the sign of optical rotation.[44]

***O*-Acetyl-(*S*)-2-hydroxy-2-(3-pyridyl)acetonitrile (1g):** Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 120 °C; detection temp. 225 °C; retention time (t_R) of 25.0 min (minor), 42.1 min (major). Spectral data were in accordance with those previously published.[14]

***O*-Acetyl-(*S*)-2-hydroxy-(2-pyridyl)acetonitrile (1h):** Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 120 °C; detection temp. 225 °C; retention time (t_R) of 27.3 min (minor), 52.6 min (major). Spectral data were in accordance with those previously published.[45]

***O*-Propionyl-(*S*)-2-hydroxy-2-phenylacetonitrile (1l):** Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 115 °C; detection temp. 225 °C; retention time (t_R) of 16.4 min (minor), 21.8 min (major). Spectral data were in accordance with those previously published.[39] The absolute configuration was determined from the sign of optical rotation.[39]

***O*-Butyryl-(*S*)-2-hydroxy-2-phenylacetonitrile (1m):** Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 115 °C; detection temp. 225 °C; retention time (t_R) of 24.8 min (minor), 28.6 min (major). Spectral data were in accordance with those previously published.[44] The absolute configuration was determined from the sign of optical rotation.[44]

***O*-Pentyryl-(*S*)-2-hydroxy-2-phenylacetonitrile (1n):** The crude product was purified by column chromatography on silica gel (eluent: EtOAc in hexanes). Yield: 85%, $[\alpha]_D^{20}$: −3.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.52$ (m, 2H, Ph), 7.45 (m, 3H, Ph), 6.43 (s, 1H, CHCN), 2.43 (dt, $J = 7.6$ Hz, 1H, $COCH_2$), 2.44 (dt, $J = 7.3$ Hz, 2H, $COCH_2$), 1.64 (ddt, $J = 7.3$, 7.6, 8.1 Hz, 2H, $CH_2CH_2CH_2$), 1.35 (tq, $J = 8.1$, 7.30 Hz, 2H, CH_2CH_3), 0.91 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 171.8$, 131.9, 130.3, 129.2, 127.8, 116.2, 62.7, 33.4, 26.6, 22.1, 13.6; MS (EI): $m/z = 217$ .10 [M^+]; anal. calcd. (%) for $C_{13}H_{15}NO_2$ (217.26): C 71.87, H 6.96, N 6.45; found: C 72.06, H 7.06, N 6.44; Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 115 °C; detection temp. 225 °C; retention time (t_R) of 42.1 min (minor), 46.9 min (major).

***O*-2-Methylbutyryl-(*S*)-2-hydroxy-2-phenylacetonitrile (1o):** The crude product was purified by column chromatography on silica gel (eluent: EtOAc in hexanes). Yield: 86%, $[\alpha]_D^{20}$: −5.2 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.52$ (m, 2H, Ph), 7.45 (m, 3H, Ph), 6.43 (s, 1H, CHCN), 2.66 [dq, $J = 7.1$, 6.8 Hz, 1H, $CH(CH_3)_2$], 1.23 (d, $J = 6.8$ Hz, 3H, CH_3), 1.19 (d, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta =$ 175.0, 132.0, 130.3, 129.2, 127.7, 116.2, 62.7, 33.7, 18.6; MS (EI): $m/z = 203.10$ [M^+]; anal. calcd. (%) for $C_{12}H_{13}NO_2$ (203.24): C 70.92, H 6.45, N 6.89; found: C 70.75, H 6.38, N 6.84; Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp. 115 °C; detection temp. 225 °C; retention time (t_R) of 18.9 min (minor), 21.0 min (major).

***O*-2,2-Dimethylbuturyl-(-(*S*)-2-hydroxy-2-phenylacetonitrile (1p):** Chiral GC, pressure 25 psi; injection temp. 225 °C; initial column temp.115 °C; detection temp. 225 °C; retention time (t_R) of 15.0 min (minor), 16.1 min (major). Spectral data were in accordance with those previously published.[39] The absolute configuration was determined from the sign of optical rotation.[39]

***O*-Cinnamoyl (*S*)-2-hydroxy-2-phenylacetonitrile (1q):** The crude product was purified by column chromatography on silica gel (eluent: EtOAc in hexanes). Yield: 89%, $[\alpha]_D^{20}$: −41.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (d, $J =$ 15.9 Hz, 1H, CH), 7.60–7.40 (m, 10H, Ph), 6.58 (s, 1H, CHCN), 6.47 (d, $J = 15.9$ Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): $\delta = 164.7$, 147.6, 133.6, 131.9, 131.0, 130.3, 129.2, 128.9, 128.3, 127.8, 116.2, 115.5, 62.8; MS (EI): $m/z = 263$ .05 [M^+]; anal. calcd. (%) for $C_{17}H_{13}NO_2$ (263.29): C 77.55, H 4.98, N 5.32; found C 76.98, H 4.64, N 4.96;[45] Chiral HPLC, 2-propanol/hexane, 1/9, flow: 0.7 mL min^{-1}, detection 212 nm retention time (t_R) of 19.5 min (major), 27.7 min (minor).

***O*-Benzoyl (*S*)-2-hydroxy-2-phenylacetonitrile (1r):** Chiral HPLC, 2-propanol/hexane 1.5/98.5, flow: 0.7 mL min^{-1}; detection 212 nm; retention time (t_R) of 16.8 min (major), 85.6 min (minor). Spectral data were in accordance with those previously published.[39] The absolute configuration was determined from the sign of optical rotation.[39]

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