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Dual Catalysis

Dual Lewis Acid/Lewis Base Catalyzed Acylcyanation of Aldehydes: A Mechanistic Study

Anna Laurell Nash,[a] Robin Hertzberg,[a] Ye-Qian Wen,[a] Björn Dahlgren,[b] Tore Brinck,[b] and Christina Moberg*[a]

Abstract: A mechanistic investigation, which included a Hammett correlation analysis, evaluation of the effect of variation of catalyst composition, and low-temperature NMR spectroscopy studies, of the Lewis acid–Lewis base catalyzed addition of acetyl cyanide to prochiral aldehydes provides support for a reaction route that involves Lewis base activation of the acyl cyanide with formation of a potent acylating agent and cyanide ion. The cyanide ion adds to the carbonyl group of the Lewis acid activated aldehyde. O-Acylation by the acylated Lewis base to form the final cyanohydrin ester occurs prior to decomplexation from titanium. For less reactive aldehydes, the addition of cyanide is the rate-determining step, whereas, for more reactive, electron-deficient aldehydes, cyanide addition is rapid and reversible and is followed by rate-limiting acylation. The resting state of the catalyst lies outside the catalytic cycle and is believed to be a monomeric titanium complex with two alcoholate ligands, which only slowly converts into the product.

Introduction

Enantioselective additions of acyl cyanides to prochiral carbonyl compounds constitute highly versatile processes, which provide access to enantioenriched O-acylated cyanohydrins. The products are useful synthetic building blocks[1] and valuable target compounds with important applications.[2] The addition of acyl cyanides to aldehydes and ketones is catalyzed by bases/nucleophiles and is accelerated by Lewis acids (LAs). It was shown already in 1949 that benzoyl cyanide added to aldehydes in the presence of base to yield cyanohydrin benzoates.[3] Other more recent examples include 1,4-diazabicyclo[2.2.2]octane (DABCO)[4] and N-heterocyclic carbene-mediated[5] acylcyanation of aldehydes, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)-catalyzed additions to ketones,[6] and additions catalyzed by Bu_3SnCN.[7] Activation of the acyl cyanide by DMSO[8] or aqueous carbonate[9] has also been shown to lead to cyanohydrin esters, in the absence of any additional catalyst. The same compounds, in racemic[10] or enantioenriched[11] forms, have also been prepared by one-pot, two-step procedures that involve acylation of cyanohydrins obtained by use of other cyanide sources, such as KCN, trimethylsilyl cyanide (TMSCN), or acetone cyanohydrin.

By use of a chiral LA in combination with an achiral tertiary amine, we were able to prepare highly enantioenriched acylated cyanohydrins from aromatic and aliphatic aldehydes and acyl cyanides derived from aliphatic acid chlorides or bromides.[12] For cases in which insufficient enantioselectivity was observed, a method incorporating in situ recycling of the minor enantiomer led to improved results.[13] Baeza et al. reported analogous products derived from aromatic acyl cyanides by employing a binol derivative equipped with tertiary amine substituents; the conditions employed did, however, not allow reaction with acetyl cyanide (**2**).[14]

In contrast to the detailed studies performed concerning the mechanism of LA-catalyzed additions of silyl cyanides[15] and cyanoformates,[16] little information is available on the acylcyanations of carbonyl compounds. Benzoylcyanation, employing the Ti^{IV} catalyst used by Baeza et al.,[14] prepared in situ from 3,3′-bis(diethylaminomethyl)-1,1′-binaphthol (binolam) and $Ti(OiPr)_4$, was suggested to be a two-step process that proceeded through the addition of HCN to the aldehyde followed by benzoylation.[17] We and others[4–6] have suggested a different mechanism, in which the nucleophile is liberated from the acyl cyanide through activation by the Lewis base (LB); the same mode of activation has been suggested for reactions with cyanoformate.[5, 18] To obtain further information on the details of the catalytic reaction, a mechanistic study has now been performed, and the results are presented herein.

Results and Discussion

As previously demonstrated, acyl cyanides react with prochiral aldehydes in the presence of titanium salen dimer **1** and a terti-

[a] Dr. A. Laurell Nash, Dr. R. Hertzberg, Dr. Y.-Q. Wen, Prof. C. Moberg
KTH Royal Institute of Technology, Department of Chemistry
Organic Chemistry 10044 Stockholm (Sweden)

[b] B. Dahlgren, Prof. T. Brinck
KTH Royal Institute of Technology, Department of Chemistry
Applied Physical Chemistry, 10044 Stockholm (Sweden)

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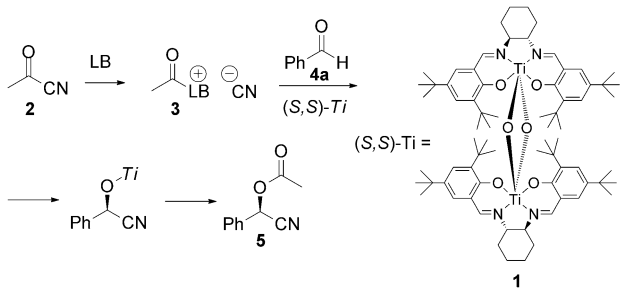
ary amine, such as triethylamine, 4-dimethylaminopyridine (DMAP), or DABCO, to give highly enantioenriched O-acylated cyanohydrins.[12] Based on a preliminary mechanistic study,[19] we proposed a mechanism for the reaction that consisted of nucleophilic attack on the LA-coordinated aldehyde by cyanide, generated by reaction of the tertiary amine with **2**, leading to a titanium alcoholate; the acetyl ammonium ion (**3**) formed along with cyanide serves as a highly efficient acylating reagent. The suggested mechanism is illustrated in Scheme 1 for the reaction of benzaldehyde (**4a**) with **2** to give acylated cyanohydrin **5**.

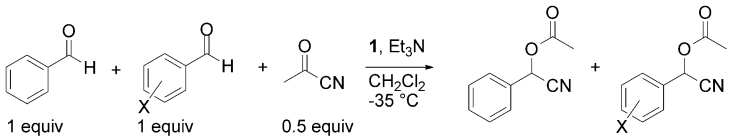
In the presence of only triethylamine, rapid product formation is observed at room temperature, whereas for an efficient reaction at −40 °C the presence of both LA and LB is required.[20,21] The mechanism proposed is in accordance with that previously suggested for the synthesis of racemic cyanohydrin esters.[4] Support for initial nucleophilic attack by the tertiary amine is available from studies of the reactivity of **2**,[22] which is known to yield substitution products with replacement of cyanide upon reaction with N-, O-, and S-nucleophiles.[23]



Scheme 1. Suggested mechanism for the addition of **2** to **4a**.

Hammett analysis

Our present investigation included a Hammett correlation study. Determination of the initial rates was nontrivial due to induction periods of different lengths for different substrates. Instead, the relative rates of the reaction of **4a** and 10 different 3- and 4-substituted arylaldehydes were determined from competition experiments.[24] The aldehydes were present in equimolar amounts and in excess relative to **2** to prevent the reactions from going to completion (Scheme 2). The experiments were performed by mixing **1** and triethylamine with **4a** and a competing aldehyde in dichloromethane. The mixtures were kept at −35 °C for 90 min before the addition of **2** to allow the formation of dimer **1** from the mixture of mono- and dimer



Scheme 2. Reaction of a substoichiometric amount of **2** with competing aldehydes.

present at ambient temperature (see below). The relative rates of the reaction of the competing aldehydes were determined as the ratio of the products formed, as analyzed by ^{1}H NMR spectroscopy.[25] A plot of $\log(k_R/k_H)$ against σ[26] resulted in a plot that exhibited a rate maximum, which was indicative of a change in the rate-determining step (Figure 1). A straight line with $\rho = 1.81$ was found for 6 of the 10 substrates. The results show that a negative charge is built up during the course of the reaction for these aldehydes, in line with rate-limiting nucleophilic attack. For the silylcyanation of aldehydes catalyzed by titanium dimer **1**, a reaction constant $\rho = 2.4$ was previously reported, whereas lower values were observed for reactions dominated by LB catalysis.[27]

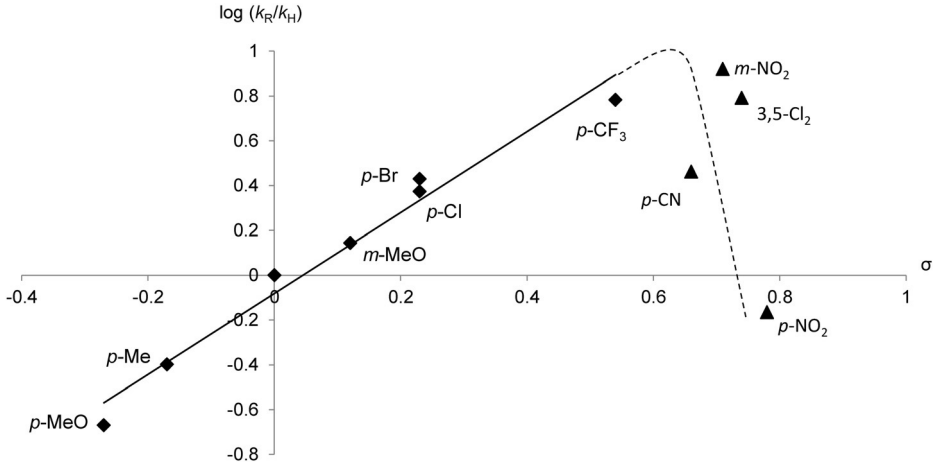


Figure 1. Hammett plot from competition experiments with **4a** and substituted benzaldehydes by using relative rates and standard σ constants. The solid straight line ($y = 1.8075 \times -0.081$; $R^2 = 0.9734$) refers to experiments with **4a** in combination with *p*-MeO-, *p*-Me-, *m*-MeO-, *p*-Br-, *p*-Cl-, and *p*-CF_3-benzaldehyde. Average values from four experiments with each substrate are reported.

For aldehydes with strongly electron-withdrawing substituents, decreasing overall reactivity was observed with increasing σ values. Adjustment to a straight line was less clear for these aldehydes than for those with lower reactivity (Figure 1), but the results suggested a transition state with an opposite electron flow in the rate-limiting step. This result is consistent with a mechanism in which acylation is rate determining instead.

The Hammett study thus indicates a change in mechanism upon going from aldehydes of low reactivity to highly reactive aldehydes. The results are consistent with two-step processes in which nucleophilic attack by cyanide is rate determining for the less reactive aldehydes and acylation for those that are highly electrophilic. For aldehydes of the latter type, attack by cyanide is accordingly a rapid, reversible step and acylation is the slow step. The suggestion is also in line with the mechanisms proposed for cyanocarbonylation of aliphatic ketones,[28] as well as acylcyanation of α-ketoesters,[29] which are based on dynamic kinetic resolution of the initially formed racemic cyanoalkoxides. The α-ketoesters were found to undergo rapid, reversible cyanation followed by slow, enantiodetermining acylation.

Three different aroyl cyanides, *p*-methoxy-, *p*-methyl, and *p*-chlorobenzoyl cyanide, were also allowed to compete with benzoyl cyanide in reactions with **4a** (Scheme 3). Although acylation is not rate determining in reactions that employ **4a** as the substrate, the reactivity of the acylating agents towards the titanium-bound alcoholate and towards the LB is reflected in the product mixture. As expected, the reactivity increased with the electrophilicity of the reagents; the ratios of k_{OMe}/k_H, k_{Me}/k_H, and k_{Cl}/k_H were 0.09, 0.30, and 4.44, respectively (see the Supporting Information).

Effect of variation of catalyst composition

If the first step constitutes a rapid, reversible cyanation, chiral LAs are expected to result in only minor enantioselection, whereas chiral LBs may lead to enantioenriched products, provided the acylating reagent contains the chiral amine. Conversely, if the first step is rate determining, chirality transfer from the LA should be more important. To test these assumptions, a series of reactions were performed by using catalytic systems composed of chiral enantiopure or racemic LAs in combination with achiral or chiral LBs. A racemic mixture of the dimeric titanium complex could, in principle, result in the formation of both homo- and heterochiral dimers. However, after stirring a 1:1 mixture of (*R*,*R*)-**1** and (*S*,*S*)-**1** in dichloromethane for 10 h, only the homochiral dimers were detected by ^{1}H NMR spectroscopy, in accordance with the known higher stability of the homodimer,[30] and therefore no heterodimers were assumed to be involved in the catalytic reactions. Use of the analogous achiral ligand derived from diaminoethane was considered to be less appropriate because this complex has been shown to adopt the heterochiral $\Delta\Lambda$-configuration and to be less reactive than (*S*,*S*)-**1**, which has the homochiral $\Delta\Delta$- or $\Lambda\Lambda$-configuration (Figure 2).[31] The results from the experiments are shown in Table 1.

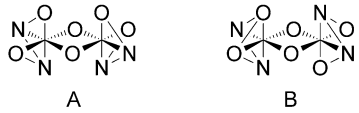
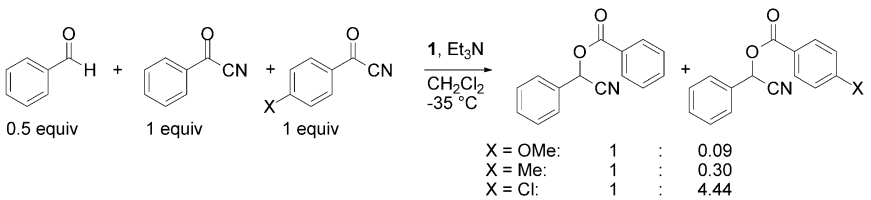


Figure 2. The syn-$\Lambda\Lambda$-configuration of C_2-symmetric homochiral dimer (*S*,*S*)-**1** (A) and S_2-symmetric achiral dimer (B).

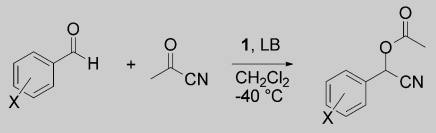
As expected from the results of the Hammett study, the LA was found to be responsible for chirality transfer in reactions with *p*-methoxy-, *p*-chloro-, and *p*-(trifluoromethyl)benzaldehyde as well as in that with the parent compound (Table 1, entries 1a–4a). In reactions with these substrates, the chiral LB had only a minor influence on *ee* (Table 1, entries 1b–4b) and close to racemic product was obtained in the presence of racemic LA and chiral LB (Table 1, entries 1c–4c). In contrast, in the reaction with 4-cyanobenzaldehyde, the presence of both enantiopure LA and chiral LB was required to obtain an enantioenriched product (Table 1, entry 5). As shown in Table 1 and Scheme 4, cinchonidine forms mismatched and matched pairs with (*R*,*R*)- and (*S*,*S*)-**1**, respectively. Although the enantiopure LA in combination with triethylamine resulted in essentially racemic product (5% *ee*; Table 1, entry 5a, and Scheme 4A), the absolute configuration of the product from reactions with triethylamine instead of cinchonidine was determined by the LA, as shown by the formation of products with the opposite absolute configuration in reactions with the two catalyst combinations (Table 1, entries 5b and c, and Scheme 4B and C). The different results of the two reactions, 41 (*S*) and 61% *ee* (*R*), respectively, demonstrate that the titanium complex has a role in chirality transfer.

If free cyanohydrin were an intermediate, as suggested by Nájera and co-workers for studies on benzoylcyanations,[17] products with the same absolute configuration and with the same *ee* would be expected in the two cases because essentially racemic product, and therefore, probably also close to



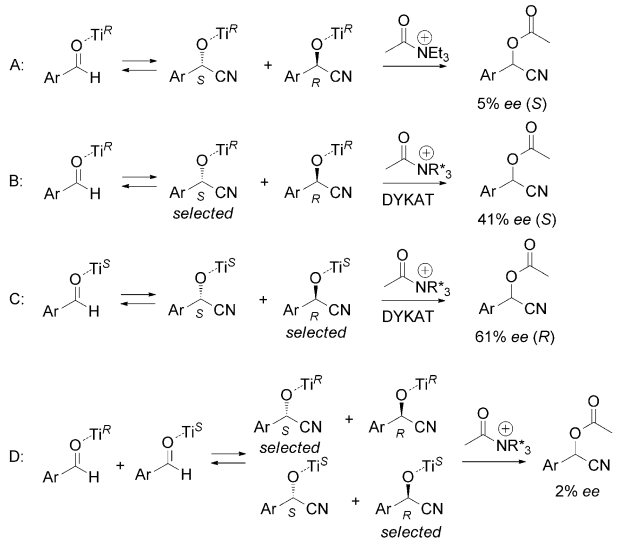
Scheme 3. Reaction of **4a** with competing aroyl cyanides.

Table 1. Enantiomeric excess (*ee*) of products from acetylcyanation catalyzed by combinations of enantiopure LA–achiral LB, enantiopure LA–chiral LB, and racemic LA–chiral LB in CH_2Cl_2 at −40 °C.



Entry	X	LA	LB	*ee* [%] (absolute configuration)	σ
1[a] a	4-OCH_3	(*R*,*R*)-**1**	NEt_3	79 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	83 (*S*)	−0.27
c		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	6 (*S*)	
2[a] a	4-H	(*R*,*R*)-**1**	NEt_3	82 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	84 (*S*)	0
b		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	6 (*S*)	
3[a] a	4-Cl	(*R*,*R*)-**1**	NEt_3	79 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	81 (*S*)	0.23
c		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	4 (*S*)	
4[b] a	4-CF_3	(*R*,*R*)-**1**	NEt_3	43 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	42 (*S*)	0.54
c		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	7 (*S*)	
5[b] a	4-CN	(*R*,*R*)-**1**	NEt_3	5 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	41 (*S*)	0.66
c		(*S*,*S*)-**1**	cinchonidine	61 (*R*)	
d		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	2 (*S*)	
6[b,c] a	3-NO_2	(*S*,*S*)-**1**	NEt_3	14 (*R*)	
b		(*S*,*S*)-**1**	cinchonidine	40 (*R*)	0.71
c		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	13 (*R*)	
7[d] a	3,5-Cl_2	(*R*,*R*)-**1**	NEt_3	27 (*S*)	
b		(*R*,*R*)-**1**	cinchonidine	74 (*S*)	0.74
c		(*S*,*S*)-**1**	cinchonidine	69 (*R*)	
d		(*S*,*S*) + (*R*,*R*)-**1**	cinchonidine	10 (*S*)	

[a] Determined by chiral GC. [b] Determined by chiral HPLC. [c] Poor peak separation. [d] Determined by HPLC; the absolute configuration is unknown, but assumed to be those indicated in analogy to products from other aldehydes.



Scheme 4. Effect of catalyst variation in the reactions of 4-cyanobenzaldehyde. A) Enantiopure LA and achiral LB; B) and C) enantiopure LA and chiral LB; D) racemic LA and chiral LB. DYKAT = dynamic kinetic asymmetric transformation.

racemic cyanohydrin, was obtained in the presence of enantiopure LA (compare the reaction with (*R*,*R*)-**1** and Et_3N; Table 1, entry 5a, and Scheme 4A). Furthermore, if decomplexation from titanium would take place prior to acylation, the product would be expected to form with the same *ee* irrespective of whether racemic (Table 1, entry 5d, and Scheme 4D) or enantiopure LA was used. The results obtained show that this is not the case, but that instead enantiopure LA is required for the formation of enantioenriched product.

The results observed for the two remaining aldehydes (Table 1, entries 6 and 7) suggest similar rates for the two steps. The conclusion from this study is that acylation occurs while the cyanohydrin is bound to titanium and that the acylating reagent is obtained by the reaction of **2** with the chiral base.

Low-temperature NMR spectroscopy studies

To further explore the course of the catalytic process and to detect possible intermediates, the reactions of both **4a** and 4-cyanobenzaldehyde with **2** in the presence of catalytic amounts of **1** and triethylamine were followed over time by low-temperature ^1H NMR spectroscopy. The reaction with 4-cyanobenzaldehyde was studied at −40 and −50 °C and that with less reactive **4a** at −40 °C. In reactions with both aldehydes, evolution of acylated cyanohydrin was observed, accompanied by a decrease in the amount of aldehyde (Figure 3). After a short induction period a new compound appeared. Because this compound started to form after the product (see the Supporting Information), it was not an intermediate, but instead a compound off the catalytic cycle. The amount of this compound was constant until most of the aldehyde was consumed; thereafter it was transformed into product. In the reaction with **4a**, this occurred after about 9–10 h, whereas in the reaction with 4-cyanobenzaldehyde at −40 °C the amount of this compound increased during the first 25 min and then decreased. The NMR spectrum of the compound formed from 4-cyanobenzaldehyde showed three signals of unequal intensity (ratio ca. 1:0.6:0.07), a major signal at $\delta = 5.57$ ppm and smaller signals at $\delta \approx 5.50$–5.53 ppm. These shifts are characteristic of benzylic cyanohydrin protons, albeit different from that of the free cyanohydrin, which appears at $\delta = 5.68$ ppm, and therefore is most likely to originate from diastereomeric titanium–cyanohydrin complexes. Other signals that appeared and disappeared together with those at $\delta \approx 5.5$ ppm were found at $\delta = 8.25$, 7.24, 7.15, and 6.66 ppm (intensity 0.3:0.5:1:0.8); additional signals may be hidden by other signals in the aromatic region. In the reaction with **4a**, a signal appeared at $\delta = 5.48$ ppm, which is close to that of free cyanohydrin, but, whereas free cyanohydrin undergoes instantaneous acylation under the reaction conditions, the compound formed in the reaction converted to product slowly. The signal at $\delta = 5.48$ ppm was flanked by only minor signals, which is consistent with the high selectivity of the first step in the reaction with this aldehyde. The yield of the compound observed reached, in both cases, close to 20% based on the aldehyde, which indicated that two molar equivalents of cyano-

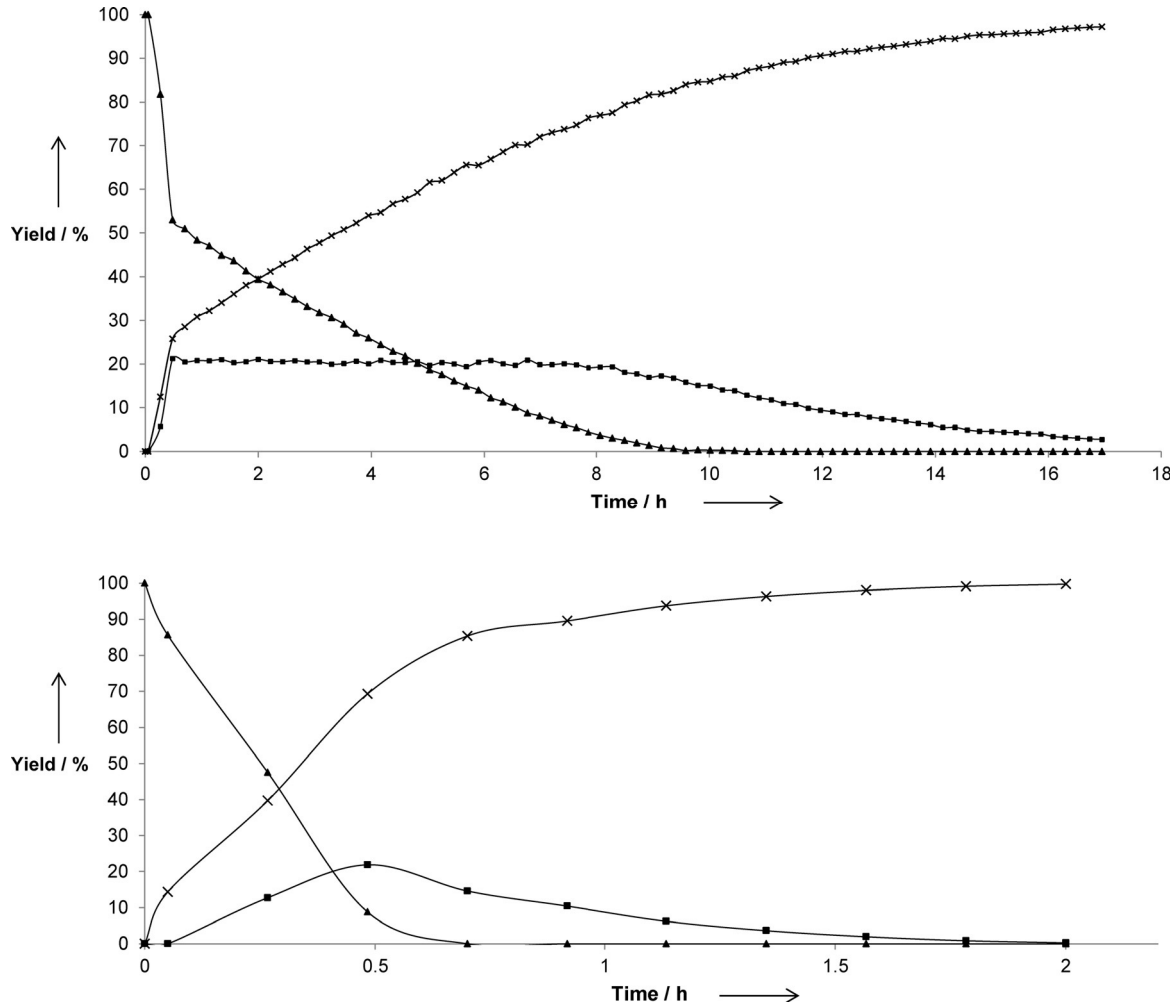


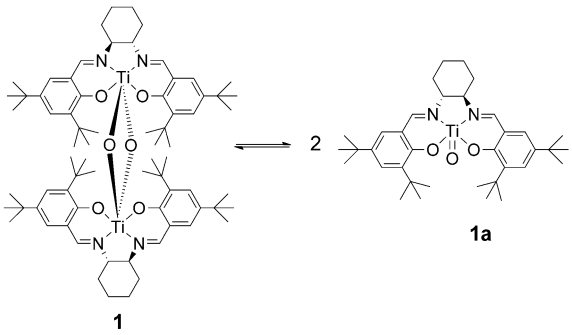
Figure 3. Formation of the titanium–cyanohydrin complex (■) and acylated product (×) and disappearance of aldehyde (▲) over time in reactions with **4a** (top) and 4-cyanobenzaldehyde (bottom) at −40 °C.

hydrin were bound to each titanium (5 mol% of dimer **1** was used in the reaction).

Influence of the order of addition of the reagents

Complex **1** is known to be in equilibrium with monomer **1a**. The dimer is favored by high concentrations and low temperatures.[16] North and co-workers demonstrated that the formation of an active catalyst was required before high *ee* could be achieved.[16] We previously found that the *ee* of the product of acylcyanation was lower in the initial phase of the reaction and then increased to a constant value.[19] We also found that a constant and higher *ee* was observed when a mixture of the titanium salen complex, aldehyde, and **2** was kept at −40 °C for 3 h prior to the addition of the LB; this was likely to result from the formation of the active catalyst.[19]

To further study the conditions under which the catalytic reaction was favored, reactions in which the reagents were added in a different order were followed by taking aliquots from the reaction mixture and analyzing the samples by GC. For this purpose, slower reacting 4-methoxybenzaldehyde was used as the substrate. When **2** was added to a mixture of aldehyde, **1**, and triethylamine, which had been stirred at −40 °C for 2 h, product formation was preceded by an induction period. When triethylamine was added last, only a short induction period was observed, and when the aldehyde was added last the reaction started almost immediately (Figure 4). These observations suggest that an active catalyst is formed prior to the reaction, and that **2** is involved in the formation of this species. Attempts to gain information about the interactions of



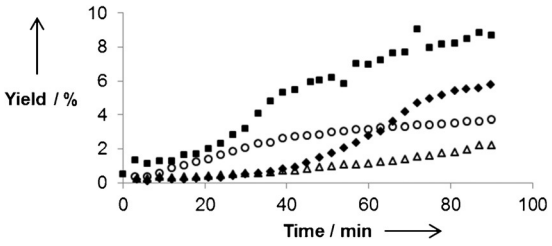


Figure 4. Kinetic experiments following the development of product from 4-methoxybenzaldehyde and **2** over time at −40 °C with different orders of addition of amine, aldehyde, and **2**. ■: NEt_3 added last, ○: aldehyde added last, and ◆: **2** added last; △: water (2.5 equiv) present.

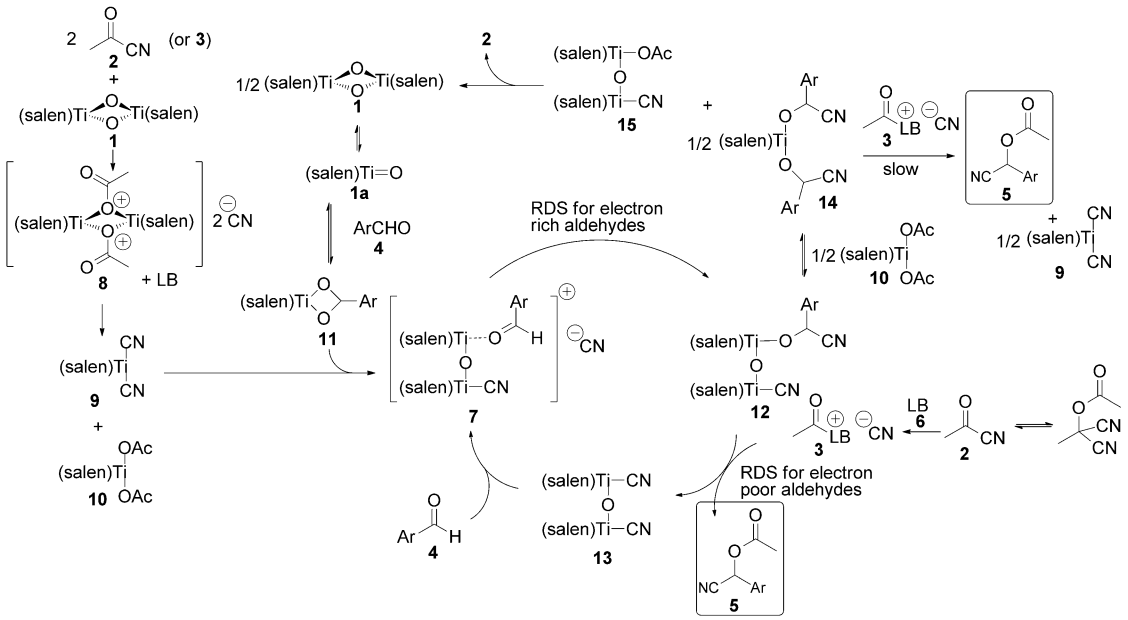
1 and **2** by low-temperature NMR spectroscopy studies were unfortunately hampered by the dimerization of **2**, which resulted in its complete consumption over 90 min. Compound **2** also undergoes base-catalyzed dimerization,[32] which is reversible, as shown by isotope scrambling when doubly ^{13}C-labeled **2** was mixed with unlabeled **2** in the presence of a catalytic amount of triethylamine.[33] When acylcyanation was performed in the presence of water (0.24–2.5 equiv), a slower reaction was observed. In contrast, water, as well as *tert*-butanol and imidazole, resulted in acceleration of the rate in acylcyanations with KCN and acetic anhydride.[10c]

Suggested mechanism

From the results presented herein, a mechanism with several features analogous to that suggested by Belokon et al. for the addition of cyanoformate to aldehydes, catalyzed by the same titanium salen dimer,[16] is proposed for the acylcyanation of prochiral aldehydes in the presence of a LB (**6**) and complex **1** (Scheme 5). The active catalyst is suggested to be **7**, obtained as previously suggested,[16] but through the replacement of ethyl cyanoformate with **2**. Thus, compound **2** or, more probably, the product obtained by the addition of the LB, **3**, reacts with **1** to give **8**, which disproportionates into **9** and **10**; bis-acetate **10** has previously been identified as a product from the reaction of **1** with acetic anhydride.[11c] The aldehyde reacts in a [2+2] cycloaddition with monomeric complex **1a** to provide metallacycle **11**; although no interaction could be detected between **4a** and **1a**, the corresponding metallacycle was observed when **4a** was replaced with hexafluoroacetone.[15] Addition of cyanide to the carbonyl function in **7** affords the neutral complex **12**, which undergoes acylation by the LB-activated acetyl cyanide (**3**) to afford the observed product **5** and **13**, which reacts with the aldehyde to complete the catalytic cycle. Complex **12** and bis-acetate **10**, obtained along with **9** during the formation of the active catalyst, are suggested to be in equilibrium with **14**, which is the off-cycle resting state of the catalyst, and complex **15**, which can be converted back into **1** and **2**. After complete consumption of the aldehyde, complex **14** is slowly converted into the product by reacting with **3**. The relative rates of attack by cyanide and acylation are a function of the reactivity of the aldehyde.

According to the mechanism shown in Scheme 5, the addition of **2** is crucial for the formation of the active catalyst. This is in agreement with the induction period observed when **2** is added after the other reagents.

The fact that most of the catalyst is transformed to **14**, serves to explain the requirement of a rather high catalyst loading, 5 mol%, for the reaction to proceed at an acceptable rate. The same high catalyst loading was also needed in cyanoformate addition, whereas silylcyanation of **4a** proceeded rapidly in the presence of merely 0.1 mol% catalyst, which suggests that the formation of an off-cycle resting state might occur also in the addition of cyanoformate.[34]



Scheme 5. Tentative mechanism suggested for LA/LB-catalyzed acylcyanation of aldehydes. RDS = rate-determining step.

In the addition of cyanocarbonate to **4a** catalyzed by titanium complex **1**, a considerably higher rate was observed when potassium cyanide was added as a cocatalyst.[35] In contrast, when the acetylcyanation of **4a** was performed in the presence of potassium cyanide, only a marginal effect on the reaction rate was observed.

The viability of Scheme 5 was investigated by numerical modeling. Although the reaction system (Table 2) has too many parameters for any fitting to be meaningful, in Figure 5 we show that the model is capable of qualitatively reproducing the data presented in Figure 3.

Table 2. Reduced reaction system corresponding to Scheme 5 (compounds **8**, **12**, and **15** are not included explicitly).

Ti_2 (**1**)	$\longleftrightarrow$	2 Ti (**1a**)
2 AcCN (**2**) + Ti_2 (**1**)	$\longrightarrow$	$TiCN_2$ (**9**) + $TiOAc_2$ (**10**)
Ti (**1a**) + A (**4**)	$\longleftrightarrow$	TiA (**11**)
TiA (**11**) + $TiCN_2$ (**9**)	$\longrightarrow$	B (**7**)
2 B (**7**) + $TiOAc_2$ (**10**)	$\longleftrightarrow$	C (**14**) + 2 Ti_2 (**1**) + 2 AcCN (**2**)
AcCN (**2**) + LB (**6**)	$\longrightarrow$	AcLB (**3**)
AcLB (**3**) + B (**7**)	$\longrightarrow$	P (**5**) + TiCNTiCN (**13**) + LB (**6**)
TiCNTiCN (**13**) + A (**4**)	$\longrightarrow$	B (**7**)
2 AcLB (**3**) + C (**14**)	$\longrightarrow$	2 P (**5**) + $TiCN_2$ (**9**) + 2 LB (**6**)

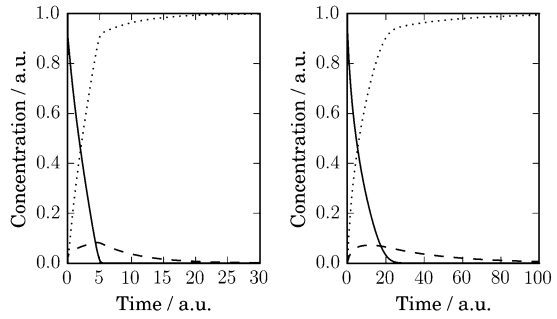


Figure 5. Modeled time evolution (^{1}H NMR spectroscopy) of the concentrations of ArCHO **4** (——), product **5** (•••••) and resting state **14** (– – –) for electron-poor (left) and -rich (right) aldehyde. In both models, the product is formed before the resting state.

In contrast, a different mechanism involving HCN was proposed by Nájera and co-workers for the reaction of aroyl cyanides with aldehydes.[17] The catalyst used was prepared in situ from the ligand and titanium tetra(isopropoxide), resulting in liberation of isopropanol. As a consequence, HCN and isopropyl benzoate were detected in the reaction mixture. The initial formation of cyanohydrin was consistent with the presence of HCN in the reaction mixture. The role of the tertiary amine was suggested to be that of a Brønsted base, thus generating free cyanide ions. This mechanism is not compatible with the results presented herein, and thus cannot be valid under our conditions. Additional evidence against a mechanism involving HCN is the lack of incorporation of ^{13}C-labeled HCN into the product.[19,36] HCN has also been ruled out as a reagent in the acetylcyanation of aldehydes by KCN and acetic anhydride catalyzed by **1**.[11a] Our results also show that **2** does not serve as the acylating agent, but that instead the acyl group is bound to the tertiary amine. These conflicting results of our studies and those by Nájera and co-workers[17] probably imply that the course of the reaction is sensitive to the reaction conditions, and that different reaction routes are followed under different conditions.

Conclusion

The results presented herein provide strong support for a mechanism for the LA–LB-catalyzed addition of acyl cyanides to prochiral aldehydes, which is analogous to that previously suggested for the addition of cyanoformate to aldehydes. The active titanium catalyst is suggested to be formed through acylation of titanium dimer **1**, either by the acyl cyanide or by the LB-activated acyl cyanide, and activation of the prochiral aldehyde by monomer **1a**. The liberated cyanide ion then adds to the LA-coordinated aldehyde. In the next step, the LA-coordinated cyanohydrin is acylated by the LB-activated acyl group. The high catalyst loading required is explained by the abundant formation of a stable titanium complex, which lies off the catalytic cycle.

Experimental Section

General

Glassware were oven-dried overnight before use. Solvents were collected from a Glass Contour solvent-dispensing system. Benzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, and triethylamine were distilled over CaH_2 prior to use. 4-Cyanobenzaldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, and 3,5-dichlorobenzaldehyde were recrystallized from ethanol. Recrystallized aldehydes, Ti complex, and cinchonidine were dried over $CaCl_2$ under vacuum prior to use. 1-Methoxynaphtalene and 4-(trifluoromethyl)benzaldehyde were purchased and used without further purification. Compounds (*S*,*S*)- and (*R*,*R*)-[{(salen)Ti-(μ-O)}$_2$][11c,30] and **2**[37] were prepared by following previously published procedures. ^{1}H NMR spectra were recorded at 500 or 400 MHz and ^{13}C NMR spectra at 100 MHz. CD_2Cl_2 used in low-temperature NMR spectroscopy studies on the evolution of product was filtered through K_2CO_3 and $MgSO_4$. Yields and enantiomeric ratios of the products were determined by GC/flame ionization detector (FID; Agilent 6850) by using the chiral column CYCLOSIL-B (30 m, 0.25 mm, 0.12 μm) and *n*-undecane as an internal standard, or by HPLC (Shimadzu LC-10AD detector SPD-10 A) with the chiral columns CHIRACEL OD-H or CHIRALPAK IC and 1-methoxynapthalene as an internal standard.

General procedure for the kinetic experiments

4-Methoxybenzaldehyde (58 μL, 0.48 mmol, 1 equiv) was added to a solution consisting of (*S*,*S*)-[{(salen)Ti-(μ-O)}$_2$] (14.6 mg, 0.0120 mmol 0.025 equiv), triethylamine (3.3 μL, 0.024 mmol 0.05 equiv), and *n*-undecane (10 μL as an internal standard) in dichloromethane (2 mL). The vial was closed with an aluminum cap with a septum. The reaction mixture was cooled to −40 °C for 2 h before cold **2** (68 μL, 0.96 mmol, 2 equiv) was added. Samples were taken every 3 min during 1.5 h and analyzed by GC/FID.

The same experimental procedure was followed for experiments with a different addition order, except that the last component was varied (aldehyde/triethylamine/**2**).

General procedure for competitive Hammett correlation experiments

Variation of the aldehyde: The experiments were performed in a glove box. (*S*,*S*)-[{(salen)Ti-(μ-O)}$_2$] (6.0 mg, 0.0049 mmol, 0.05 equiv) was dissolved in dichloromethane (0.5 mL). Compound **4a** (10 μL, 0.098 mmol, 1 equiv) and the competing aldehyde (0.098 mmol, 1 equiv) were added to the solution followed by triethylamine (1.4 μL, 0.0099 mmol, 0.1 equiv). The reaction mixture was cooled to −35 °C for 60 min before cold **2** (3.4 μL, 0.049 mmol, 0.5 equiv) was added. The reaction mixture was kept at that temperature for 18 h before the reaction was quenched by filtering the cold reaction mixture through silica, followed by elution with diethyl ether. After evaporation of the solvents, the crude mixture was analyzed by ^{1}H NMR spectroscopy. The relative rates of the reactions were determined as the ratio of products formed. When possible, the *ee* value of the products in the crude mixture was determined by chiral GC (see the Supporting Information).

Variation of the aroyl cyanide: The experiments were performed in a glove box. (*S*,*S*)-[{(salen)Ti-(μ-O)}$_2$] (6.0 mg, 0.0049 mmol, 0.05 equiv) was dissolved in dichloromethane (0.2 mL) in a small vial. Compound **4a** (5 μL, 0.05 mmol, 0.5 equiv) and triethylamine (1.4 μL, 0.0099 mmol, 0.1 equiv) were added and the solution was cooled to −35 °C for 60 min. A precooled mixture of benzoyl cyanide (13 mg, 0.1 mmol, 1 equiv) and the competing aroyl cyanide (0.1 mmol, 1 equiv) in dichloromethane (0.3 mL) was added to the reaction vial. The reaction mixtures were kept at −35 °C for 18 h. The reaction was quenched by filtering the cold reaction mixture through a short silica plug followed by elution with diethyl ether. The organic mixture was washed twice with an aqueous solution of $NaHCO_3$ to remove the excess aryl acids formed. The two phases were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was analyzed by ^{1}H NMR spectroscopy. The relative rates of the reactions were determined as the ratio of products formed.

General procedure for experiments combining enantiopure LA and achiral LB

The reaction mixtures were prepared in a glove box, transferred to a fume hood, and cooled to −40 °C. (*R*,*R*)-[{(salen)Ti-(μ-O)}$_2$] (14.6 mg, 0.0120 mmol, 0.05 equiv) was dissolved in dichloromethane (1 mL), and triethylamine (3.3 μL, 0.024 mmol, 0.1 equiv) was added followed by the aldehyde (0.24 mmol, 1 equiv). 1-Methoxynapthalene (10 μL) or *n*-undecane (10 μL) was added as an internal standard. The reaction vial was closed with an aluminum cap with a septum and cooled to −40 °C for 60 min prior to the addition of cold **2** (34 μL, 0.48 mmol, 2 equiv). After 18 h at −40 °C, the cold reaction mixture was transferred to a saturated solution of ammonium chloride. The two phases were separated and the organic phase was filtered through a silica plug prior to evaporation of the solvent. The crude product was analyzed by chiral GC or HPLC and ^{1}H NMR spectroscopy.

General procedure for experiments combining enantiopure LA and chiral LB

The reactions were performed as described above by using a catalyst prepared from (*R*,*R*)-[{(salen)Ti-(μ-O)}$_2$] (14.6 mg, 0.0120 mmol, 0.05 equiv) and cinchonidine (7.0 mg, 0.024 mmol, 0.1 equiv).

General procedure for experiments combining racemic LA and chiral LB

The reactions were performed as described above by using a catalyst prepared from (*R*,*R*)-[{(salen)Ti-(μ-O)}$_2$] (7.3 mg, 0.0060 mmol, 0.025 equiv), (*S*,*S*)-[{(salen)Ti-(μ-O)}$_2$] (7.3 mg, 0.0060 mmol, 0.025 equiv), and cinchonidine (7.0 mg, 0.024 mmol, 0.1 equiv).

Low-temperature NMR spectroscopy studies

(*S*,*S*)-[{(salen)Ti-(μ-O)}$_2$] (6.0 mg, 0.0049 mmol, 0.05 equiv) was dissolved in CD_2Cl_2 (0.5 mL) and cooled to −40 °C for 2 h. The aldehyde (0.10 mmol, 1 equiv), triethylamine (1.4 μL, 0.010 mmol, 0.1 equiv), 1-methoxynapthalene (10 μL, used as an internal standard), and **2** (14 μL, 0.20 mmol, 2 equiv) were added at −78 °C. ^{1}H NMR spectra were recorded every 13 min at −40 °C (see the Supporting Information).

Numerical modeling

Numerical modeling was performed by using the COPASI (a complex pathway simulator)[38] 4.15 program. All rate laws were assumed to follow the law of mass action.

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