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Mechanistic studies on the enantioselective BINOLAM/titanium(IV)-catalyzed cyanobenzoylation of aldehydes. Part 1.

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Alejandro Baeza,[a] Carmen Nájera,[a*] José M. Sansano, [a] and José M. Saá, [b*]

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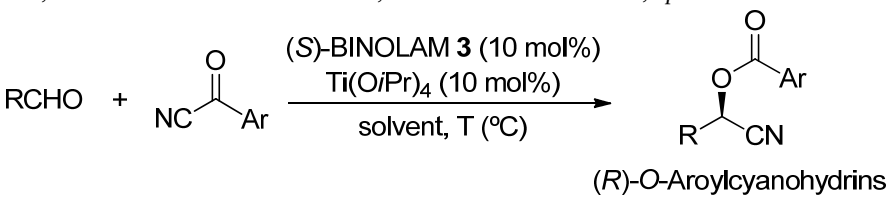

(*R*)-*O*-Aroylcyanohydrins

Stereochemistry Abstract

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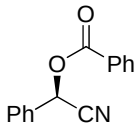

$C_{15}H_{12}NO_2$

(*R*)-2-(Benzoyloxy)-2-phenylacetonitrile

Source of chirality: (*S*)-Binolam

68% *ee*

$[\alpha]^{25}_{D}$= +7.7 (*c* 2.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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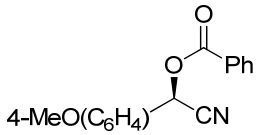

$C_{16}H_{13}NO_2$

(*R*)-2-(Benzoyloxy)-2-(4-methoxyphenyl)acetonitrile

Source of chirality: (*S*)-Binolam

56% *ee*

$[\alpha]^{25}_{D}$= +10.9 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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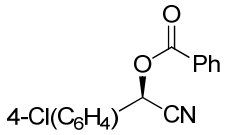


$C_{15}H_{10}ClNO_2$:

(*R*)-2-(Benzoyloxy)-2-(4-chlorophenyl)acetonitrile.

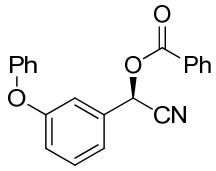
Source of chirality: (*S*)-Binolam

58% *ee*

$[\alpha]^{25}_{D}$= +9.6 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá



$C_{21}H_{15}O_3N$

(*R*)-2-(Benzoyloxy)-4-(3-phenoxyphenyl)acetonitrile

Source of chirality: (*S*)-Binolam

66% *ee*

$[\alpha]^{25}_D$= + 17.5 (*c* 1.5, $CHCl_3$)

Absolute stereochemistry (*R*)

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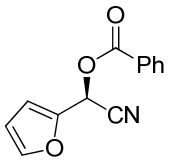

$C_{13}H_9NO_3$

(*R*)-2-(Benzoyloxy)-2-furylacetonitrile

Source of chirality: (*S*)-Binolam

55% *ee*

$[\alpha]^{25}_D$ = +2.9 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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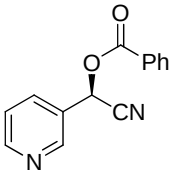

$C_{14}H_{10}N_2O_2$

2-(Benzoyloxy)-2-(3-pyridyl)acetonitrile

Racemic

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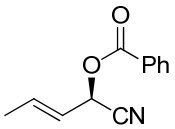

$C_{12}H_{11}NO_2$

(2*R*,3*E*)-2-(Benzoyloxy)pent-3-enenitrile

Source of chirality: (*S*)-Binolam

65% *ee*

$[\alpha]^{25}_D$= -4.5 ºC (*c* 1.3, CHCl3)

Absolute stereochemistry (*R*)

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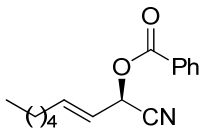

$C_{16}H_{19}NO_2$

(*R*)-2-(Benzoyloxy)non-3-enenitrile

Source of chirality: (*S*)-Binolam

68% *ee*

$[\alpha]^{25}_D$ = -4.3 (*c* 0.5, $CHCl_3$)

Absolute stereochemistry (*R*)

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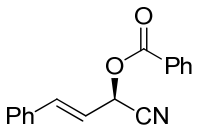

$C_{17}H_{13}O_2N$

(2*R*,3*E*)-2-(Benzoyloxy)-4-phenylbut-3-enenitrile

Source of chirality: (*S*)-Binolam

82% *ee*

$[\alpha]^{20}_D$= +7.5 (*c* 1.4, $CHCl_3$)

Absolute stereochemistry (*R*)

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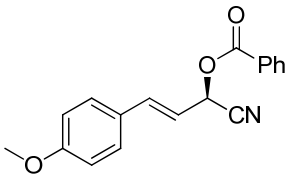

$C_{18}H_{15}O_3N$

(2*R*,3*E*)-2-(Benzoyloxy)-4-(4-methoxyphenyl)but-3-enenitrile

Source of chirality: (*S*)-Binolam

76% *ee*

$[\alpha]^{20}_{D}$= +3.9 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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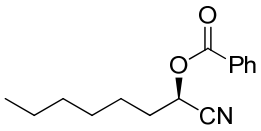

$C_{19}H_{14}NO_2$

(*R*)-2-(Benzoyloxy)octanenitrile

Source of chirality: (*S*)-Binolam

58% *ee*

$[\alpha]^{25}_{D}$= +10.1 (*c* 0.7, $CHCl_3$)

Absolute stereochemistry (*R*)

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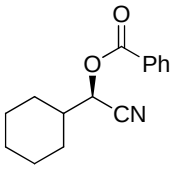

$C_{15}H_{17}NO_2$

(*R*)-2-(Benzoyloxy)-2-cyclohexylacetonitrile

Racemic

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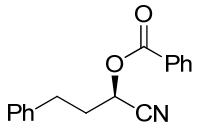

$C_{17}H_{16}NO_2$

(*R*)-2-(Benzoyloxy)-4-phenylbutanenitrile

Source of chirality: (*S*)-Binolam

65% *ee*

$[\alpha]^{25}_D$= +13.9 (*c* 2.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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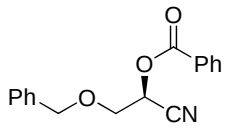

$C_{17}H_{15}O_3N$

(*R*)-2-(Benzoyloxy)-3-benzyloxypropanenitrile

Source of chirality: (*S*)-Binolam

38% *ee*

$[\alpha]^{25}_D$= + 10.1 (*c* = 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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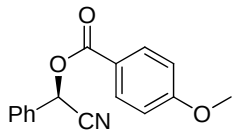

$C_{16}H_{13}NO_3$

(*R*)-2-(4-Methoxybenzoyloxy)-2-phenylacetonitrile

Source of chirality: (*S*)-Binolam

55% *ee*

$[\alpha]^{25}_D$= +12.1 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

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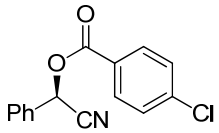

$C_{15}H_{10}ClNO_2$

(*R*)-2-(4-Chlorobenzoyloxy)-2-phenylacetonitrile

Source of chirality: (*S*)-Binolam

58% *ee*

$[\alpha]^{25}_{D}$= +6.9 (*c* 1.0, $CHCl_3$)

Absolute stereochemistry (*R*)

Tetrahedron Asymmetry
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Mechanistic studies on the enantioselective BINOLAM/titanium(IV)-catalyzed cyanobenzoylation of aldehydes. Part 1

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ABSTRACT

The enantioselective titanium(IV)-catalyzed cyanobenzoylations of aldehydes using 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixtures as precatalyst gives rise to *O*-aroyl cyanohydrins **4** with good enantiomeric excesses. Unfortunately, the standard optimization set carried out on the assumption of Curtin-Hammett behavior, led to no amelioration.

Extensive experimental and computational studies have now been carried out with the purpose of identifying the key mechanistic aspects governing enantioselectivity. HCN and isopropyl benzoate were detected in the reacting mixtures. This as well as the reaction response to the presence of an exogenous base, and the failure to react in the presence of Binol:Ti(OiPr)$_4$ mixtures, led us to propose not a direct but an indirect process involving an enantioselective hydrocyanation step followed by *O*-benzoylation. Computational work carried with mononuclear monomeric $\mathbf{M_M}$ and dinuclear mixed dimer $\mathbf{D_{IMD}}$ as catalysts support this mechanistic proposal.

On the other hand, cyanobenzoylations carried out with 1:2 or higher 1:n (up to 1:5) BINOLAM:Ti(O*i*Pr)$_4$ mixtures appear to involve an striking reversal of enantioselection. This, together with the fact that benzoylation of ligated *i*PrOH is a slow reaction, has led us to conclude that our cyanobenzoylations do not fit within the standard Curtin-Hammett kinetic scheme. Instead, our BINOLAM:Ti(O*i*Pr)$_4$ - catalyzed cyanobenzoylations of aldehydes rather behave as non-Curtin-Hammett kinetic schemes. Further computational analysis is needed in order to make a clear-cut distinction between Curtin-Hammet and non-Curtin-Hammett kinetic frameworks.

1. Introduction

Accessing enantiomerically enriched cyanohydrins and their *O*-functionalized derivatives is a goal of major synthetic interest.[1] For this purpose both chiral Lewis acids, chiral Lewis bases and dual catalysts have been successfully employed.[2] Specifically, we have explored the use of metal complexes of the bifunctional ligand BINOLAM (*R*)-**1a** and (*S*)-**1a** [(*R*)- or (*S*)-3,3'-bis(diethylaminomethyl)-1,1'-binaphthol] as catalysts for the enantioselective cyanation of aldehydes.[3] These studies revealed that aluminium-derived catalysts generated in situ by reacting BINOLAM with Me_2AlCl, generally represented as "BINOLAM-AlCl", worked as efficient catalysts for the direct enantioselective cyanosilylations,[4] cyanophosphorylations,[5] and cyanoalkoxycarbonylations of aldehydes.[6]

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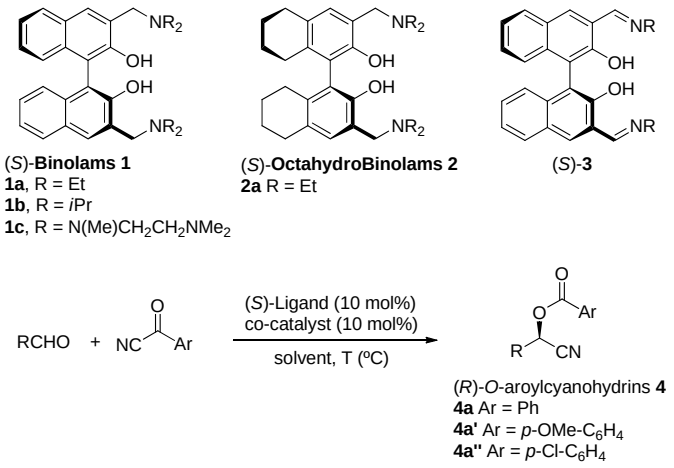
Unfortunately though, most of the above cyanating reagents are moisture sensitive and therefore their use for large scale enantioselective cyanations must be avoided. The less hydrolizable acyl cyanides seemed to be a good choice in light of their well-known capacity to promote the cyanoacylation of aldehydes.[7] Accordingly, we decided to explore the enantioselective cyanoacylations of aldehydes using acyl cyanides as the reagents of choice. Much to our dismay, our previously successful "BINOLAM-AlCl" complexes were of no value for cyanoacetylations or cyanobenzoylations as neither one of these reactions took place, even in the presence of a substoichiometric amount of water, ethyl alcohol, water-containing molecular sieves 4Å or triphenylphosphane oxide. Instead, we explored "BINOLAM-TiX_2" complexes resulting from of a 1:1 mixture of BINOLAM **1a** and Ti(O*i*Pr)$_4$ as catalysts for the cyanoacylation of aldehydes (3-phenylpropanal and benzaldehyde were initially employed as representative substrates). The results of this investigation have been communicated.[8] At the time of this preliminary communication, the detailed mechanism of action of "BINOLAM-TiX_2" complexes as catalysts was lacking, among other reasons because the structure of titanium(IV) complexes was not well-known,[9] in spite of recent advances in the field.[10] We would like now to fully describe "BINOLAM-TiX_2" catalyzed cyanobenzoylations and illustrate some mechanistic aspects that we believe are of general validity for other catalyzed reactions. In particular, we claim that the stubborn difficulty in optimizing some catalyzed reactions might be related to the fact that they do not fit within the usual Curtin-Hammett kinetic construction. More specifically, we will illustrate by means of combined experimental and computational studies that "BINOLAM-TiX_2" catalyzed cyanobenzoylations actually take place by means of an indirect process involving an enantioselective hydrocyanation, followed by *O*-benzoylation, which appear not to behave as a non-Curtin-Hammett kinetic system.[11]



Scheme 1. Catalytic systems employed for the enantioselective cyanobenzoylation of aldehydes

2. Results and Discussion

We explored some time ago the enantioselective synthesis of *O*-acylcyanohydrins **4** promoted by "BINOLAM-TiX_2" species. In particular, extensive experimentation was carried out using enantiomerically pure ligands **1-3**, different titanium(IV) sources [either Ti(O*i*Pr)$_4$, Ti(O*i*Pr)$_2$Cl$_2$ or Ti(OMe)$_4$], different acylating reagents (acetyl cyanide, benzoyl cyanide and related aroyl cyanides), solvents (THF, toluene or CH_2Cl_2), additives (MS4Å, *i*PrOH, Ph_3PO), and eventual fine-tuning of the common reaction variables, as well as the ligand:titanium ratio. Actually, best results were obtained when operating in THF at room temperature with titanium-derived catalysts prepared in situ from 1:1 BINOLAM **1a**:Ti(O*i*Pr)$_4$ mixtures in the presence of aroyl cyanides (incomplete conversions were observed when acetyl cyanide was employed). It is worth noting that these reactions responded to the ligand-accelerated catalysis concept as only trace amounts of product could be observed when using Ti(O*i*Pr)$_4$ (10% mol) alone.[12] The desired *O*-aroyl (for the most part *O*-benzoyl) cyanohydrins **4** were thus obtained in good yield and an encouraging 84:16 enantiomeric ratio (for the case of benzaldehyde) or 83:17 for the case of 3-phenylpropanal.[8] These results were considered worthy being further pursued for improvement (Scheme 1) and thus we became involved in a careful, Curtin-Hammett based, optimization process.

As illustrated in Table 1, the scope of the reaction was shown to be wide (applicable to aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes), with some limitations though. Particularly relevant is the case of α-substituted aldehydes (cyclohexanecarbaldehyde) which yielded almost racemic product (Table 1, entry 16). Also worth being noted is that the presence of basic heteroatoms in the substrate led to a decrease in enantioselectivity (Table 1, entries 10 and 18). In all cases the absolute configuration of *O*-benzoylcyanohydrins **4** was determined by comparing their optical rotations with those of samples prepared by *O*-benzoylation of enantiopure cyanohydrins. In addition, we showed that the chiral ligand could be easily recovered after workup and successfully reused (Table 1, entry 3).

Table 1. Enantioselective synthesis of *O*-aroylcyanohydrins **4** by reaction of aroyl cyanides ArCOCN with aldehydes RCHO in the presence of a 1:1 BINOLAM **1a**:Ti(O*i*Pr)$_4$ mixture.

Ent.	R	Ar	t (h)	**4**	Yield (%)[a]/*er*[b]
1	Ph	Ph	6	(*R*)-**4a**	91/*84:16*[c]
2	Ph[d]	Ph	6	(*S*)-**4a**	90/*16:84*[c]
3	Ph[e]	Ph	6	(*R*)-**4a**	90/*84:16*[c]
4	Ph	4-(MeO)C_6H_4	24	(*R*)-**4a'**	75/*78:22*[c]
5	Ph	4-ClC_6H_4	72	(*R*)-**4a''**	87/*79:21*[c]
6	4-(MeO)-C_6H_4	Ph	21	(*R*)-**4b**	76/*79:21*
7	4-Cl-C_6H_4	Ph	18	(*R*)-**4c**	85/*79:21*
8	3-(PhO)-C_6H_4	Ph	22	(*R*)-**4d**	92/*83:17*
9	2-Furyl	Ph	7	(*S*)-**4e**	89/*78:22*
10	3-Pyridyl	Ph	22	(*R*)-**4f**	93/*64:36*[f]
11	(*E*)-MeCH=CH	Ph	17	(*R*)-**4g**	78/*83:17*
12	(*E*)-C_5H_{11}CH=CH	Ph	6	(*R*)-**4h**	87/*84:16*[g]
13	(*E*)-PhCH=CH	Ph	24	(*R*)-**4i**	75/*92:8*
14	(*E*)-4-(MeO)-C_6H_4CH=CH	Ph	60	(*R*)-**4j**	71/*88:12*
15	n-C_6H_{13}	Ph	12	(*R*)-**4k**	80/*78:22*[h]
16	Cyclohexyl	Ph	8	(*R*)-**4l**	83/*56:44*
17	$PhCH_2CH_2$	Ph	3	(*R*)-**4m**	93/*83:17*[f]
18	$PhCH_2OCH_2$	Ph	2	(*R*)-**4n**	85/*69:31*

[a] Isolated yields after flash chromatography. [b] Determined by HPLC using chiral columns (Daicel, Chiralpack AS). [c] Determined by HPLC using chiral columns (Daicel, Chiralpack AS). [d] (*R*)-BINOLAM [(*R*)-**1a**] was used. [e] Recovered ligand (*S*)-**1a** after one batch was employed. [f] Determined by HPLC using chiral columns (Daicel, Chiralcel OD-H). [g] Determined by HPLC using chiral columns (Daicel, Chiralcel OJ). [h] Determined by GC using a chiral column (γ-cyclodextrin).

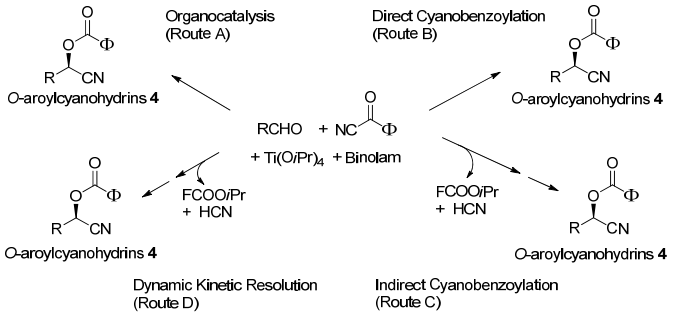
Within the framework of a Curtin-Hammett catalytic cycle the adventure of optimizing a specific enantioselective catalytic procedure is, in general, a self-consistent adjustment of operational variables (reagents, temperature, solvent, time, additives, etc). Initially we took for granted the Curtin-Hammett behaviour of our Ti(IV)-catalyzed methodology.[13] However, the difficulties in further improving the encouraging, though nevertheless insuperable, (84:16) enantiomeric ratio reached in the above titanium(IV)-catalyzed cyanobenzoylations drove us to carry out both experimental and, eventually, computational mechanistic studies upon the "BINOLAM-TiX_2"-catalyzed cyanobenzoylation,[11] with the aim of learning on those mechanistic intricacies that could help us in improving their efficiency and perhaps of related reactions as well.[14]

Kinetic studies on titanium(IV) alkoxide catalysis are difficult to carry out due to their tendency to form aggregates. Accordingly, we focused our attention in evaluating the competing catalytic routes with the purpose of undergoing a rational, Curtin-Hammett-based optimization of "BINOLAM-TiX_2"-catalyzed cyanobenzoylations.

2.1. Mechanistic studies: the competing catalytic routes.

As illustrated in Scheme 2 four possible competing routes were conceived feasible for the observed cyanobenzoylations, the first being the organocatalytic route A. Since BINOLAMs **1** are bis tertiary amines, we envisioned them as plausible organocatalysts capable of promoting enantioselective cyanations by means of a Lewis base mechanism.[15] However, this mechanistic alternative was soon rejected because BINOLAM **1a** in the absence of a metallic cocatalyst was found to be unable to promote the benzoylcyanation of benzaldehyde (Table 2, entry 1). Instead, we judged probable that the observed asymmetric cyanobenzoylation of aldehydes promoted by BINOLAM:Ti(O*i*Pr)$_4$ mixtures could be the result of a Ti(IV)-catalyzed asymmetric process, either through a direct cyanobenzoylation (route B) or, perhaps, through an indirect process involving hydrocyanation by the action of HCN followed by *O*-benzoylation (route C). Alternatively, enantiomerically enriched *O*-benzoylcyanohydrins **4** could result from a dynamic kinetic resolution (route D) of racemic cyanohydrins involving "BINOLAM-TiX_2"-catalyzed *O*-benzoylation. However, the attempted kinetic resolution of a racemic sample of mandelonitrile under the above optimized conditions led to racemic **4a**. Consequently, the titanium(IV)-catalyzed kinetic resolution (route D) was also disregarded as an operating route in our cyanobenzoylations. Accordingly, we were left with routes B and C, only.

The so-called indirect cyanobenzoylation (route C) calls for the intervention of a substoichiometric amount of HCN in the stereochemically relevant hydrocyanation step, which should then be followed by *O*-acylation of the resulting chiral cyanohydrin, thereby regenerating the HCN required for a subsequent cycle. For the hydrocyanation step, one could conceive catalysis taking place either through an LABB type mechanism or through a titanium cyanate or isocyanate intermediate. As pointed out by Spencer *et al*., trace amounts of Brønsted acids derived from hydrolysis of Lewis acids are in many cases the actual catalysts for many so-called "Lewis acid-catalyzed reactions".[16] By analogy, the cyanide derivatives used as reagents in cyanation reactions could well be the source of HCN due to inevitable partial, or trace, hydrolysis undergone during manipulation. In previous work we,[17,18,19] and other groups,[20,21] reported positive proves for the presence of HCN in the solution mixtures employed for titanium-catalyzed and aluminium-catalyzed cyanosilylations (110,5 ppm in $CDCl_3$),[18] cyanophosphorylations (112,3 ppm in $CDCl_3$),[17] and cyanoalkoxycarbonylations (109,8 ppm in $CDCl_3$).[19] An additional, indirect prove for the implication of HCN in the enantioselective processes catalyzed by "BINOLAM-AlCl" is the dramatic loss of *ee* when reactions were carried in the presence of an exogenous base such as Et_3N, as in this case the LABB dual role of the catalyst should be severely disabled due to the competing action of an external Brønsted base (BB).



Scheme 2. Plausible catalytic routes for the BINOLAM:Ti(O*i*Pr)$_4$ enantioselective cyanobenzoylation of aldehydes.

On the other hand, the direct cyanobenzoylation (route B) is generally assumed to involve a highly reactive chiral, *N*-acylium cyanide intermediate species capable of adding to the carbonyl group thereby giving rise to the final *O*-functionalized cyanohydrin either in a single step, or stepwise. In this case, catalysis should be of the LALB type. A recent report by Moberg et al. regarding a specific Ti(IV)-catalyzed acylcyanation of aldehydes called for a direct acylcyanation,[22] as there were no Brønsted acids (ROH, H_2O, etc) available neither on the catalyst, nor in the reaction medium. The main support for this proposal was the lack of incorporation of ^{13}C when $H^{13}CN$ was bubbled through the reaction solution prior to introduction of the reagents. We rejected, however, carrying out such an experiment as the literature clearly points out that the $H^{13}CN$ carefully prepared from $K^{13}CN$ and 85% H_3PO_4 and eventually distilled under extremely careful conditions is in fact a solution of $H^{13}CN$ in water in a 1:2 molar ratio.[23] Under these conditions our catalytic reaction would be quenched, thereby leading to useless conclusions.

With this in mind, we decided to look first for the direct detection of HCN in "BINOLAM-TiX_2"-catalyzed benzoylcyanation reactions under the experimental conditions of operation. Provided the presence of HCN could be demonstrated, we planed to confront both the direct and indirect routes (B and C, respectively) by means of a computational study, aiming at identifying the actual mechanism of our cyanobenzoylations.

Actually, the ^{13}C NMR spectrum of the solution mixture employed for cyanobenzoylations (i.e., a 1:1 mixture of BINOLAM and Ti(O*i*Pr)$_4$ in the presence of an equivalent amount of commercial benzoyl cyanide) in deuterated chloroform showed a very small signal at 111,8 ppm (see below) which was shown to correspond to HCN (as expected, a somewhat larger signal was observed when CD_3CN was used as solvent, as this solvent is usually contaminated with water). Since commercial benzoyl cyanide does not contain dissolved HCN according to ^{13}C NMR measurements, the above observation must be the consequence of the reaction of *i*PrOH (either free or ligated to titanium) with benzoylcyanide. *O*-benzoylcyanides **4** were

obtained in high chemical yield under these conditions (Table 2, entries 3 and 4). In agreement with this, when the experimental conditions were modified so as to incorporate vacuum removal of *i*PrOH prior to addition of benzoyl cyanide, we found a quite inefficient reaction (50% yield) even after 45 hr reaction time (Table 2, entry 6). Moreover, the attempted cyanobenzoylations carried out with a 1:1 BINOLAM:Ti(O*i*Pr)$_2$Cl$_2$ mixture ended up in no reaction being observed (Table 2, entry 7), a result consistent with the irreversible protonation of the amino groups by the HCl produced during complexation. It thus becomes inevitable to consider the likely implication of HCN in the above "BINOLAM-TiX$_2$"-catalyzed cyanobenzoylation reactions, a scenario in which the amino arms of our "BINOLAM-TiX$_2$" catalyst ought to play a relevant role.

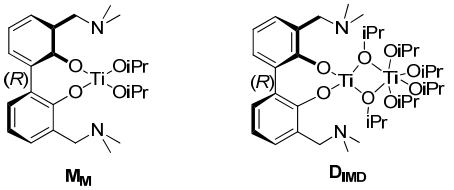
Table 2. Optimization of reaction conditions for cyanoaroylation of aldehydes RCHO with aroyl cyanides catalyzed by 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixtures.

Ent.[a]	R	Ligand/Additive/Co-catalyst/Solvent/Time	Yield (%)[b]/ *er*[c]
1	Ph	**1a**/none/none/THF/5 h	(0)/—
2	Ph	none/none/Ti(O*i*Pr)$_4$/THF/ 24h	(<5[d])/—
3	Ph	**1a**/none/Ti(O*i*Pr)$_4$/THF/ 5 h	(>95)/*84:16*
4	Ph(CH$_2$)$_2$	**1a**/none/Ti(O*i*Pr)$_4$/THF/ 5 h	(>95)/*83:15*
5	Ph	**1a**/iPrOH(10% mol)/Ti(O*i*Pr)$_4$/THF/7 h	(>70)/*64:36*
6	Ph	**1a**/none/Ti(O*i*Pr)$_4$/THF/ 45 h	(50[e])/*84:16*
7	Ph	**1a**/none/TiCl$_2$(O*i*Pr)$_2$/ CH$_2$Cl$_2$/48 h	(0)/—
8	Ph	Binol/none/Ti(O*i*Pr)$_4$/THF/ 72 h	(0)/—
9	Ph	**1a**/Et$_3$N(10% mol)/Ti(O*i*Pr)$_4$/ THF/5 h	(>95)/*63:37*
10	Ph	**1a**/Et$_3$N(50% mol)/Ti(O*i*Pr)$_4$/ THF/5 h	(>95)/*54:46*
11	Ph	**1a**/Et$_3$N(100% mol)/ Ti(O*i*Pr)$_4$/THF/45 min	(>95)/*50:50*

[a] The general procedure for cyanoaroylation of aldehydes involves treatment of a THF(dry) solution of aldehyde, at room temperature, under argon, with 3 equivalents of aroyl cyanide in the presence of 10 mol % of Ti(O*i*Pr)$_4$ and 10% mol% of (*R*) or (*S*)-BINOLAM **1a**. [b] Crude yields of *O*-aroyl cyanohydrins were determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC using chiral columns (Daicel, Chiralpack AS). [d] 10 mol % of Ti(O*i*Pr)$_4$ [e] *i*PrOH was removed under vacuum.

To further elucidate the role, if any, of the catalyst amino arms we carried out an experiment using Binol instead of BINOLAM, under otherwise identical conditions. This experiment ended in no reaction being observed (Table 2, entry 8), thus suggesting a key role for those amino groups.[8] Furthermore, the addition of exogenous triethylamine to the 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixture employed for the cyanobenzoylation of aldehydes gave rise to a significant lowering of the *er* value. Actually, addition of 0, 10, 50 or 100 mol% of Et$_3$N, led to a straightforward decline of the enantiomeric ratio (84:16, 63:37, 54:46 and 50:50, respectively), again pointing to hydrocyanation by HCN (Table 2, entries 3, 9, 10, 11) as the major event (route C) in our Ti(IV)-catalyzed cyanobenzoylations. This erosion of the *er* promoted by the addition of an external tertiary amine is in line with a significant rise of the background reaction, as supported by the observed rate acceleration after addition of 100 mol% Et$_3$N (reaction was over in ca. 45 min, as shown in Table 2, entry 11). To further evaluate this mechanistic proposal (route C) we carefully examined the NMR spectrum of a 1:1 mixture of BINOLAM and benzoyl cyanide, and also of a 1:1:1 mixture of BINOLAM:Ti(O*i*Pr)$_4$:benzoyl cyanide, at room temperature. The conclusion from the first of these experiments is simple: there is no observable interaction between BINOLAM and benzoyl cyanide, as revealed by a ^{1}H NMR spectrum taken after a short period of time, in agreement with the fact that BINOLAM **1a** itself does not promote the benzoylcyanation of benzaldehyde (Table 1, entry 1). As mentioned above, when Ti(O*i*Pr)$_4$ was added to this mixture, we immediately noticed the formation of a very small amount of HCN (broad peak centred at 111.8 ppm) and of isopropyl benzoate (relevant signals appearing at 21.0, 68.0, 175.8 ppm) in the ^{13}C NMR spectrum of the mixture. Isopropyl benzoate was also detected in this mixture by GC-MS analysis. This is consistent with the idea that the initial complexes formed in a 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixture slowly react with benzoyl cyanide thereby giving rise to the actual catalysts and HCN. As expected, reaction of a 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixture with benzoyl chloride took place much faster.

Thus, conditions for indirect benzoylcyanations (route C) indeed exist in our reaction mixture. Nevertheless, the existence of HCN does not invalidate the occurrence of the *N*-benzoyl ammonium cyanide species required for a direct benzoylcyanation (route B). To discriminate between them, we looked for computational evidence, for which purpose we examined prototype mononuclear $\mathbf{M_M}$ and dinuclear $\mathbf{D_{MD}}$ Ti(IV) complexes, as illustrated in Scheme 3. The absence of non-linear effects in cyanobenzoylations carried out with 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixtures (see experimental section) indicates that only mononuclear monomeric $\mathbf{M_M}$ and dinuclear mixed dimers $\mathbf{D_{MD}}$ can actually intervene as catalysts. Accordingly, we choose mononuclear titanium derivative $\mathbf{M_M}$.2iPrOH and $\mathbf{D_{IMD}}$.2iPrOH for this computational test.[11] Ion pair $\mathbf{M_M}$COPh$^+$NC$^-$ (resulting from the reaction of $\mathbf{M_M}$.2iPrOH with 3 equivalents of PhCOCN) and the corresponding aldehyde complex $\mathbf{M_M}$COPh$^+$NC$^-$.CH$_3$CHO were found to be stationary points at the B3LYP/6-31G* level of calculation. Unfortunately though, we were unable to find (at both the HF ab initio and DFT levels of calculations) the transition structures corresponding to the direct benzoylcyanation (route B). We explored also the dinuclear mixed dimer $\mathbf{D_{IMD}}$ as catalyst for the direct benzoylcyanation reactions (route B). Eventually, we found the transition structure for the direct benzoylcyanation, namely $\mathbf{D_{IMD}}$COPh$^+$NC$^-$ts. This transition structure was computed to lie 30,95 kcal/mol higher than that corresponding to the indirect benzoylcyanation, namely $\mathbf{M_M}$-ts (relevant energy data are given in Table 3). We can then conclude that the most favourable route for enantioselective "BINOLAM-TiX$_2$" catalyzed cyanobenzoylations should be that of the indirect process (route C) which calls for the intervention of an enantioselective hydrocyanation by means of HCN followed by an stereochemically inert *O*-benzoylation.



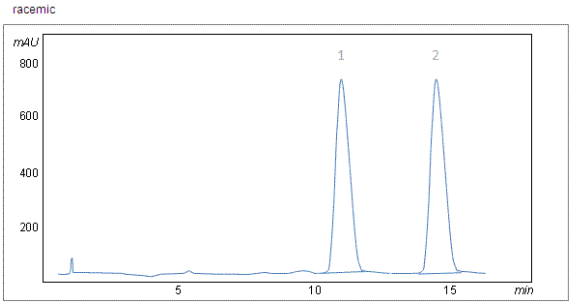
$\mathbf{M_M}$ $\mathbf{D_{IMD}}$

Scheme 3. Monomeric **M** and dimeric titanium(IV) **D** derivatives computationally evaluated as benzoylcyanation catalysts.

Table 3. Evaluation of direct (route B) vs. indirect cyanobenzoylation (route C) by DFT (B3LYP/6-31G*) calculations.

Entry	Reactants	Relative energies in kcal/mol and absolute energies in hartrees (*in italics*)
1	$\mathbf{M_{IMD}}$PhCO.CN-ts$_{Si}$ + biphelam + 2PhCOO*i*Pr + 2HCN	+10,04 *-6637,273770*
2	2biphelam + 2Ti(OiPr)$_4$ + 3PhCOCN + CH_3CHO	0 *-6637,289775*
3	$\mathbf{M_{IMD}}$-ts$_{Si}$ + biphelam + 2PhCOO*i*Pr + HCN + □COCN	−14.39 *-6637,312699*
4	$\mathbf{M_M}$-ts$_{Si}$ + **8**.2(*i*PrOH) + HCN + 2PhCOO*i*Pr	−20.91 *-6637,323097*

Since, as shown above, HCN is generated in situ by reaction of the aroyl cyanide with *i*PrOH (either free or ligated), and most important, this appeared to be a slow process, at this point we realized that our experimental conditions might not be leading us to a Curtin-Hammett kinetic scheme. Instead, cyanobenzoylations could actually take place under a non-Curtin-Hammett framework where the precatalytic BINOLAM-titanium complexes initially formed should be converted to the actual catalysts by reacting with benzoyl cyanide. The most relevant consequence deriving from this new set of conditions is the striking differences one could find in optimizing a non-Curtin-Hammett instead of a Curtin-Hammett system. Thus, whereas optimization of the latter generally involves a self-consistent adjustment of operational variables (temperature, solvent, concentration of reagents, time, etc), that of a non-Curtin-Hammett mechanism may be quite hard to achieve due to the fact that a kinetic quench of the active catalytic routes occur in this case. Accordingly, optimization of a non-Curtin-Hammett mechanism may require the modification of structural variables namely ligand modification, change of metal derivative, etc).[11]



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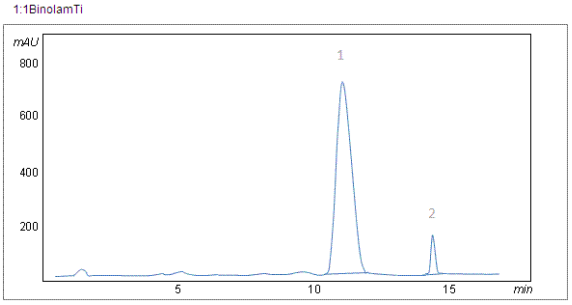
2	14.333	34668.1	729.5	50.005



#	Time	Area	Height	Area%
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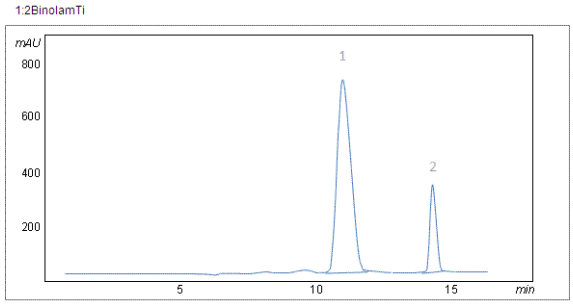

#	Time	Area	Height	Area%
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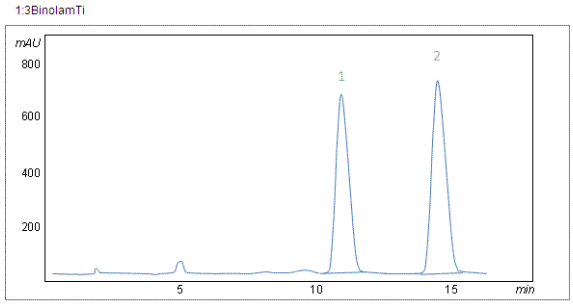

#	Time	Area	Height	Area%
1	11.589	32545.9	673.4	48.093
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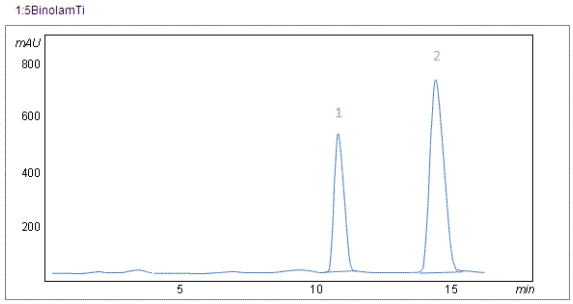

#	Time	Area	Height	Area%
1	11.556	26001.6	560.2	41.783
2	14.320	36228.1	769.2	58.216

Figure 1. HPLC chromatograms of *O*-benzoylcyanohydrin **4a** resulting from cyanobenzoylation reactions catalyzed by 1:1 *rac*-BINOLAM:Ti(O*i*Pr)$_4$ and 1:n *(S)*-BINOLAM:Ti(O*i*Pr)$_4$ mixtures (n=1, 2, 3, 5).

It was thus of major importance to find out whether or not our Ti(IV)-catalyzed cyanobenzoylations could be definitely categorized as Curtin-Hammett or non-Curtin-Hammett kinetic systems. A straightforward comparative analysis (Table 4) of cyanobenzoylations carried out with 1:1 BINOLAM:Ti(O*i*Pr)$_4$ mixtures,[8] with those employing 1:2 and higher (1:n) ratios, provided evidence indicative of the existence of, at the very least, two competing routes leading to opposite enantioselectivities.[24] A reversal of enantioselection is apparent in going from 1:1, to 1:5 BINOLAM:Ti(O*i*Pr)$_4$ ratios as illustrated in the HPLC chromatograms provided in Fig.1. One can expect some erosion of enantioselectivity by the background reaction that takes place when using excess Ti(O*i*Pr)$_4$, but definitely not a reversal of enantioselectivity. In fact, only trace amounts (<5%) of racemic *O*-benzoylcyanohydrin **4a** resulted when benzaldehyde was submitted to benzoylcyanation in the presence of 10% molar Ti(O*i*Pr)$_4$ (Table 2, entry 2) as the only catalyst. We therefore conclude that at the very least two competitive routes having opposite enantioselectivities operate in our cyanobenzoylations. With the final objective of finding the appropriate conditions for

an efficient enantioselective cyanobenzoylation, we consider of prime importance to properly identify these competing routes. Due to the difficulty in carrying out kinetic studies upon Ti(IV)-catalyzed reactions, we plan to recourse to a detailed computational study as the most reliable plan to reach our goal.[11]

Table 4. Dependence of benzoylcyanation enantioselectivity upon BINOLAM:Ti(O*i*Pr)$_4$ ratios

Binolam:Ti(O*i*Pr)$_4$ ratio	Reaction time (h)	Conversion (%)	*er*	Configuration of major enantiomer of **6a**
1:1	5	95	*84:16*	(*R*)
1:2	6	98	*69:31*	(*R*)
1:3	5	90	*48:52*	(*R*)
1:5	7	90	*42:58*	(*S*)

3. Conclusions

The exploration of the enantioselective benzoylcyanation of aldehydes using less reactive cyanide derivatives such as aroyl cyanides, catalyzed by BINOLAM:Ti(O*i*Pr)$_4$ mixtures, turned out to be a difficult job because the optimization armoury employed on the assumption of a Curtin-Hammett kinetic framework, did not work properly. We thus planned to carry out a mechanistic study. Among the various mechanistic schemes examined as plausible routes, only the direct (route B) and indirect (route C) cyanobenzoylations were found to be real possibilities according to experimental facts. A short term computational analysis carried out upon mononuclear $\mathbf{M_M}$ and dinuclear $\mathbf{D_{lMD}}$ models allowed us to establish that the so-called indirect cyanobenzoylation route should be faster than the direct cyanobenzoylation route, at least for our reaction conditions. Therefore, cyanobenzoylations promoted by BINOLAM:Ti(O*i*Pr)$_4$ mixtures can be described as indirect processes (route C) taking place by means of an enantioselective hydrocyanation followed by *O*-benzoylation. Interestingly, examination of the results of cyanobenzoylations carried out with 1:1, 1:2 or higher 1:n BINOLAM:Ti(O*i*Pr)$_4$ ratios led us to observe a striking reversal of enantioselection. This, together with the fact that benzoylation of ligated *i*PrOH is a somewhat slow reaction, has led us to conclude that our cyanobenzoylations might not fit within the classical Curtin-Hammett kinetic scheme. We plan to recourse to a detailed computational study to clearly identify Curtin-Hammett and non-Curtin-Hammett frameworks,[11,25] with the goal of finding an efficient enantioselective method for the cyanoacylation of aldehydes.

4. Experimental section

4.1. General methods

All reactions were carried out under argon, including the transfer of the solid reagents to the reaction vessel. Anhydrous solvents were freshly distilled under argon atmosphere and commercial aldehydes were also distilled prior to use. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IRs were recorded on a Nicolet 510 P-FT and only the structurally most relevant peaks are listed. NMR spectra were performed on a Bruker AC-300 using CDCl3 as solvent and TMS as internal standard unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a Shimadzu LC-10AD and Jasco PU2000 Plus series equipped with the corresponding chiral column (Chiralcel OD, and OD-H and Chiralpack AD and AS) described for each compound, using mixtures of n-hexane/isopropyl alcohol as mobile phase. Chiral GC analysis was performed on a HP-5890 using a WCOT γ-cyclodextrin column. Retention times of the major enantiomer are given in boldface. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on a Shimadzu QP-5000 and high resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm).

4.2. General procedure for the cyanobenzoylation of aldehydes catalyzed by 1:1 BINOLAM:Ti(OiPr)4 mixtures

To a solution of (*R*)-, or (*S*)-BINOLAM (0.025 mmol, 11.4 mg), in dry THF (1 mL), under a dried atmosphere of argon, titanium tetraisopropoxide (0.025 mmol, 9 μL) was added, the resulting suspension being stirred for 1 h at room temperature. Freshly distilled aldehyde (0.25 mmol) and the aroyl cyanide (0.75 mmol, 90 μL) were then added. The reaction was monitored by ^{1}H NMR or GC. When it was judged complete, HCl 2M (2 mL) and ethyl acetate (2 mL) were added, and the mixture was stirred for an additional 10 minutes. The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated under vacuum, and the remaining crude material was purified by flash chromatography to yield pure benzoyl-*O*-cyanohydrin **4** in yields reported in main text and Table 1. The aqueous layer was treated with a 1M NH_3 /1M NH_4Cl buffer solution and then extracted with ethyl acetate (2x10 mL). The organic layers were dried ($MgSO_4$) and after filtration evaporated under vacuum to yield (*S*)-BINOLAM in 96% (11mg). When using *p*-methoxybenzoyl cyanide and *p*-chlorobenzoyl cyanide, under otherwise identical conditions, compounds **4a'** and **4a''** were obtained. The optical purity of the enantiomerically enriched **4** was then determined by HPLC or GC using chiral columns. Their physical and analytical data are given below.

4.2.1. (*R*)-2-(Benzoyloxy)-2-phenylacetonitrile 4a. Colorless oil; $[\alpha]^{25}_D$= +7.7 (*c* 2.0, $CHCl_3$) (68% *ee*); TLC: R_f 0.51 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2343, 1731, 1246, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$): δ_H 6.7 (s, 1H, CHO), 7.44-7.49 (m, 5H, ArH), 7.60-7.64 (m, 3H, ArH), 8.06-8.08 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CHCl_3$): δ_C 63.3 (CH), 116.2 (CN), 127.8, 128.1, 128.6, 129.3, 130.1, 130.4, 131.8, 134.1 (ArC), 164.6 (CO); MS (EI): m/z 237 (M^+, 15%), 116 (41), 105 (100); HRMS calcd. for $C_{15}H_{12}NO_2$: 237.0790, found: 237.0800; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, hexane/2-propanol, 99/1, 1.0 mL/min, t_r= **11.6** and 14.3 min.

4.2.2. (*R*)-2-(Benzoyloxy)-2-(4-methoxyphenyl)acetonitrile 4b. Colorless oil; $[\alpha]^{25}_D$= +10.9 (*c* 1.0, $CHCl_3$) (56% *ee*); TLC: R_f 0.67 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2351, 1731, 1246, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.84 (s, 3H, OCH_3), 6.62 (s, 1H, CHCN), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.45 (t, J = 7.6, 1H, ArH), 7.55 (d, J = 8.8 Hz, 2H, ArH), 7.60-7.65 (m, 1H, ArH), 8.04 (m, 3H, ArH); ^{13}C NMR (75 MHz): δ_C 55.4 (CH_3), 63.1 (CHCN), 114.6 (ArC), 116.4 (CN), 123.9, 128.6, 129.7, 130.0, 132.0, 134.0, 161.1 (ArC), 164.7 (CO); MS (EI): m/z 267 (M^+, 14.3%), 146 (51), 147 (51), 136 (54), 135 (100), 105 (43); HRMS calcd for $C_{16}H_{13}NO_2$: 267.0895; found: 267.0889; HPLC: DAICEL CHIRALPAK AD, λ = 254 nm, n-hexane/2-propanol, 99/1, 1 mL/min, t_r = **25.7** and 29.1 min.

4.2.3. (*R*)-2-(Benzoyloxy)-2-(4-chlorophenyl)acetonitrile 4c. Colorless oil; $[\alpha]^{25}_D$= +9.6 (*c* 1.0, $CHCl_3$) (58% *ee*); TLC: R_f 0.45 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2346, 1732, 1257 and 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.60 (s, 1H, CHO), 7.37-7.43 (m, 4H, ArH), 7.51-7.56 (m, 3H, ArH), 7.98 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl3): δ_C 62.6 (CH), 115.8 (CN), 128.4, 128.7, 129.3, 129.6, 130.1, 130.4, 134.2, 136.7 (ArC), 164.5 (CO); MS (EI): m/z 271 (M^+, 12%), 150 (34), 105 (100); HRMS calcd for $C_{15}H_{10}ClNO_2$: 271.0400; found: 271.0401; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, n-hexane/2-propanol, 99.5/0.5, 0.5 mL/min, t_r = **44.7** and 47.4 min.

4.2.4. (*R*)-2-(Benzoyloxy)-4-(3-phenoxyphenyl)acetonitrile 4d. Colorless oil; $[\alpha]^{25}_D$= + 17.5 (*c* 1.5, $CHCl_3$) (66% *ee*); TLC: R_f 0.47 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2245, 1733, 1247, 1088 cm^{-1}; ^1H RMN (300 MHz, $CDCl_3$): δ_H 6.62 (s, 1H, CHCN), 7.06 (m, 3H, ArH), 7.16 (t, J = 6,9 Hz, 1H, ArH), 7.32-7.39 (m, 4H, ArH), 7.46 (m, 3H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 8.06 (d, J = 7.8 Hz, 2H, ArH); ^{13}C RMN (75 MHz, $CDCl_3$): δ_C 62.8 (CHCN), 115.9 (CN), 117.6, 119.4, 120.0, 122.0, 124.1, 128.0, 128.6, 129.9, 130.1, 130.6, 133.6, 134.1, 156.1, 158.2 (ArC), 164.5 (CO); MS (EI): m/z 329 (M^+, 12,4%), 181 (9), 114 (8), 106 (9), 105 (100); HRMS calcd for $C_{21}H_{15}O_3N$: 329.1052, found: 329.1051; HPLC: DAICEL CHIRACEL OD-H, λ= 254 nm, n-hexane/2-propanol, 95/5, 1 mL/min,, t_r= 12,1 and **13,5** min.

4.2.5. (*R*)-2-(Benzoyloxy)-2-furylacetonitrile 4e. Colorless oil; $[\alpha]^{25}_D$ = +2.9 (*c* 1.0, $CHCl_3$) (55% *ee*); TLC: R_f 0.39 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2339, 1731, 1255, 1085, 1600, 1585, 1496, 1452, 1315, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.46-6.48 (m, 1H, CH=CHO), 6.75 (s, 1H, CHCN), 6.77 (d, J = 3.4 Hz, 1H, CH=C), 7.47 (t, J = 7.6 Hz, 2H, ArH), 7.54 (m, 1H, C=CHO), 7.60-7.65 (m, 1H, ArH), 8.07 (d, J = 7.2 Hz, 2H, Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 61.6 (CHCN), 111.1 (CH=C), 112.8 (CH=CHO), 114.2 (CN), 127.8, 128.6, 130.1, 134.2 (ArC), 144.2 (CCHCN), 145.1 (C=CO), 164.4 (CO); MS (EI): m/z 227 (M^+, 15%), 182 (42), 106 (60), 105 (100); HRMS calcd. for $C_{13}H_9NO_3$: 227.0582, found: 227.0588; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, n-hexane/2-propanol, 99/1, 1 mL/min, tr = 12.3 and **14.7** min.

4.2.6. (*R*)-2-(Benzoyloxy)-2-(3-pyridyl)acetonitrile 4f. White powdered solid; m p: 66 ºC (from n-hexane/ethyl acetate); TLC: R_f 0.31 (n-hexane/ethyl acetate, 3/2); IR (KBr): ν_{max} 2244, 1724, 1258, 1091, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.74 (s, 1H, CHCN), 7.46-7.51 (m, 3H, ArH), 7.59-7.67 (m, 1H, ArH), 8.01-8.13 (m, 3H, ArH), 8.78 (br s, 1H, ArH), 8.92 (b s, 1H, ArH) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 61.2 (CHCN), 115.3 (CN), 127.6, 128.3, 128.7, 130.1, 133.1, 134.4, 135.8, 148.8, 151.3 (ArC), 164.3 (CO); MS (EI): m/z 238 (M^+, 3.4%), 183 (35), 117 (35), 105 (100); Anal. calcd for $C_{14}H_{10}N_2O_2$: C 70.6, H 4.2 and N 11.8%; found: C 70.3, H 4.3 and N 11.4%; HPLC: DAICEL CHIRALCEL OD-H, λ = 254 nm, n-hexane/2-propanol, 96/4, 1 mL/min, t_r = **26.7** and 30.5 min.

4.2.7. (*2R,3E*)-2-(Benzoyloxy)pent-3-enenitrile 4g. Colorless oil; $[\alpha]^{25}_D$= -4.5 ºC (*c* 1.3, CHCl3) (65% *ee*); TLC: R_f 0.55 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2240, 1732 1259, 1090, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.79 (d, J = 6.2 Hz, 3H, CH3), 6.10 (dd, J = 6.6, 1.6. Hz, 1H, C=CHCO), 6.18 (d, J = 6.7 Hz, 1H, CHCN), 6.20-6.32 (m, 1H, CH_3CH=C), 7.47 (t, J = 7.6 Hz, 2H, ArH), 7.60-7.65 (m, 1H, ArH), 8.06 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.7 (CH3), 61.9 (CHCN), 115.8 (CN), 121.4 (C=CHCO), 128.2, 128.6, 130.0, 133.9 (ArC), 135.9 (CH2CH=CH), 164.6 (CO); MS (EI): m/z 201 (M^+, 2.3%), 105 (100), 77 (27); HRMS calcd for $C_{12}H_{11}NO_2$: 201.0790, found: 201.0790; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, n-hexane/2-propanol, 99.5/0.5, 1 mL/min, t_r = 7.1 and **8.1** min.

4.2.8. (*R*)-2-(Benzoyloxy)non-3-enenitrile 4h. Colourless oil; $[\alpha]^{25}_D$ = -4.3 (*c* 0.5, $CHCl_3$) (68% *ee*); TLC: R_f 0.65 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2339, 1732, 1258, 1089, 1600 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ_H 0.89 (t, J = 6.9 Hz, 3H, CH_3), 1.28-1.47 (m, 6H, 3xCH_2), 2.12-2.19 (m, 2H, CH_2CH=CH), 5.67 (dd, J = 15.4, 6.6 Hz, 1H, C=CHCHO), 6.07 (d, J = 6.6 Hz, 1H, CHCN), 6.20-6.29 (m, 1H, C=$CHCH_2$), 7.47 (t, J = 7.6 Hz, 2H, ArH), 7.60-7.65 (m, 1H, ArH), 8.06 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.0 (CH_3), 22.4, 29.7, 31.3, 32.0 (CH_2), 62.0 (CHCN), 115.9 (CN), 120.0 (C=CHCO), 128.1, 128.6, 130.0, 133.9 (ArC), 141.0 (CH_2CH=CH), 164.6 (CO); MS (EI): m/z 257 (M^+, 0.3%), 125 (7), 105 (100), 77 (18); HRMS calcd for $C_{16}H_{19}NO_2$: 257.1416, found: 257.1411; HPLC: DAICEL CHIRALCEL OJ, λ = 254 nm, n-hexane/2-propanol, 93/7, 1 mL/min, t_r = 6.5 and **7.4** min.

4.2.9. (2*R*,3*E*)-2-(Benzoyloxy)-4-phenylbut-3-enenitrile 4i. Colourless oil; $[\alpha]^{20}_D$= +7.5 (*c* 1.4, $CHCl_3$) (82% *ee*) ; TLC: R_f 0.49 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2226, 1732, 1246, 1089, 1601 cm^{-1}; ^1H RMN (300 MHz, $CDCl_3$): δ_H 6.28-6.37 (m, 2H, CHCN, CH=CHCO), 7.07 (m, 1H, CHPh), 7.35-7-65 (m, 8H, ArH), 8.08 (deform. d, J = 8.1 Hz, 2H, ArH); ^{13}C RMN (75 MHz, $CDCl_3$): ^{13}C RMN (75 MHz, $CDCl_3$): δC 62.0 (CH), 115.5 (CN), 118.4, 127.2, 128.3, 128.6, 128.8, 129.4, 130.2, 134.1, 134.4, 138.0 (ArC), 164.6 (CO); MS (EI): m/z 263 (M^+, 9%), 141 (28), 140 (21), 115 (30), 105 (100); HRMS calcd for $C_{17}H_{13}O_2N$: 263.0946, found: 263.0971. HPLC: DAICEL CHIRACEL OJ, λ= 254 nm, n-hexano/2-propanol, 93/7, 1 mL/min, t_r= **29.7** and 42.5 min.

4.2.10. (2*R*,3*E*)-2-(Benzoyloxy)-4-(4-methoxyphenyl)but-3-enenitrile 4j. Colourless oil; $[\alpha]^{20}_D$= +3.9 (*c* 1.0, $CHCl_3$) (76% *ee*); TLC: R_f 0.46 (n-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2238, 1730, 1606, 1252, 1088 cm^{-1}; ^1H RMN (300 MHz, $CDCl_3$): δ_H 3.83 (s, 3H, OCH_3), 6.18 (dd, J = 15.4, 6.9, Hz, 1H, CHCHCN), 6.24 (d, J = 6.9 Hz, 2H, CHCN), 6.90 (d, J = 8.6 Hz, 2H, ArH), 7.01 (d, J = 15.4 Hz, 1H, PhCH=CH), 7.39 (t, J = 8.6 Hz, 1H, ArH), 7.48 (t, J = 7.8 Hz, 2H, ArH), 7.63 (t, J = 7.8 Hz, 1H, ArH), 8.07 (m, 2H, ArH); ^{13}C RMN (75 MHz, $CDCl_3$): δ_C 55.3 (CH_3), 62.3 (CHCN), 114.2 (ArC), 115.8 (CN), 116.0 (CHCHCN), 127.1 (ArC), 128.3 (PhCH=CH), 128.5, 128.6, 130.0, 134.0, 137.8, 160.1 (ArC), 164.7 (CO); MS (EI): m/z 293 (M^+, 34%), 188 (18), 171 (60), 156 (20), 128 (18), 122 (24), 105 (100); HRMS calcd for $C_{18}H_{15}O_3N$: 293.1052, found: 293.1075; HPLC: DAICEL CHIRALPAK AS, λ= 260 nm, n-hexane/2-propanol, 98/2, 1 mL/min, t_r= 30.4 and **38.0** min.

4.2.11. (*R*)-2-(Benzoyloxy)octanenitrile 4k. Colourless oil; $[\alpha]^{25}_D$= +10.1 (*c* 0.7, $CHCl_3$) (58% *ee*); TLC: R_f 0.29 (*n*-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2345, 1739, 1266, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.90 (t, *J* = 6.7 Hz, 3H, CH_3), 1.26-1.45 (m, 6H, 3xCH_2), 1.53-1.63 (m, 2H, CH_2), 2.04 (dd, *J* = 15.6, 6.7 Hz, 2H, CH_2CH), 5.58 (t, *J* = 6.7 Hz, 1H, CHO), 7.48 (t, *J* = 7.4 Hz, 2H, ArH), 7.63 (t, *J* = 7.4 Hz, 1H, ArH), 8.06 (d, *J* = 7.2 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14 (CH_3), 22.4, 24.6, 28.5, 31.4, 32.4 (CH_2), 61.6

(*C*H), 117.0 (CN), 128.3, 128.6, 130.0, 134.0 (ArC), 164.8 (CO); MS (EI): *m/z* 246 (M^+ + 1, 0.1%), 123 (36), 122 (34), 105 (100); HRMS calcd for $C_{19}H_{14}NO_2$: 245.1416; found: 245.1417; CG: WCOT γ-CD (stationary phase FS-Lipodex-E, 0.25 μm), $T_{injector}$ = 250 ºC, $T_{detector}$ = 260 ºC, T_{column} = 90 ºC (5 min) to 180 ºC (0.6 ºC/min.), P= 120 KPa, t_r = **152.5** and 152.9 min.

4.2.12. (*R*)-2-(Benzoyloxy)-2-cyclohexylacetonitrile 4l. Colourless prisms; m p: 101 ºC (from n-hexane/ethyl acetate); TLC: R_f 0.56 (n-hexane/ethyl acetate, 4/1); IR (KBr): ν_{max} 2243, 1720, 1262, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.19-1.33 (m, 6H, CH_2), 1.72-2.01 (m, 5H, CH_2 + $CHCH_2$), 5.44 (d, J = 5.8 Hz, 1H, CH-CN), 7.48 (t, J = 7.6 Hz, 2H, ArH), 7.63 (t, J = 7.6 Hz, 1H, ArH), 8.05 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.3, 25.4, 25.7, 28.0, 28.2 (CH2), 40.3 (CHCHCN), 66.0 (CHCN), 116.2 (CN), 128.4, 128.6, 129.9, 133.9 (ArC), 164.8 (CO); MS (EI): m/z 244 (M^+, 0.1%), 161 (15), 123 (20), 121 (31), 105 (100); Anal. calcd for $C_{15}H_{17}NO_2$: C 74.1, H 7.0 and N 5.8%; found: C 73.8, H 6.8 and N 5.8%; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, n-hexane/2-propanol, 99.5/0.5, 0.7 mL/min, t_r = **11.3** and 13.1 min.

4.2.13. (*R*)-2-(Benzoyloxy)-4-phenylbutanenitrile 4m. Colourless oil; $[\alpha]^{25}_D$= +13.9 (*c* 2.0, $CHCl_3$) (65% *ee*); TLC: R_f 0.40 (*n*-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2333, 1731, 1263, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.35-2.43 (m, 2H, CH_2CHO), 2.93 (t, *J* = 7.6 Hz, 2H, CH_2Ph), 5.53 (d, *J* = 6.7 Hz, 1H, CHO), 7.19-7.25 (m, 3H, ArH), 7.31-7.34 (m, 2H, ArH), 7.47 (t, *J* = 7.5, 2H, ArH), 7.60-7.65 (m, 1H, ArH), 8.01 (d, *J* = 7.2, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.8 (*C*H_2CHO), 33.9 (*C*H_2Ar), 61.0 (*C*H), 116.7 (CN), 126.7, 128.1, 128.3, 128.6, 129.8, 130.0, 134.0, 139.0, (ArC), 164.7 (CO); MS (EI): *m/z* 266 (M^+ + 1, 0.05%), 143 (100), 116 (20), 105 (32); HRMS calcd for $C_{17}H_{16}NO_2$ (M^+ + 1): 266.2181, found: 266.2183; HPLC: DAICEL CHIRACEL OD-H, λ = 254 nm, *n*-hexane/2-propanol, 95/5, 1.0 mL/min, t_r = 14.1 and **16.0** min.

4.2.14. (*R*)-2-(Benzoyloxy)-3-benzyloxypropanenitrile 4n. Colourles oil; $[\alpha]^{25}_D$= + 10.1 (*c* 1.0, $CHCl_3$) (38% *ee*); TLC: R_f 0.27 (*n*-hexane/ethyl acetate, 4/1); IR (neat): ν_{max} 2247, 1732, 1262, 1092 cm^{-1}; ^1H RMN (300 MHz, $CDCl_3$): δ_H 3.91 (d, *J* = 5.5 Hz, 2H, C*H*$_2$CH), 4,66 (d, *J* = 3.0 Hz, 2H, C*H*$_2$O), 5.75 (t, *J* = 5.5 Hz, 1H, CHCN), 7.29-7.35 (m, 5H, ArH), 7.47 (t, *J* = 7.6 Hz, 2H, ArH), 7.60 (t, *J* = 7.5 Hz, 1H, ArH), 8.04 (d, *J* = 7,2 Hz, 2H, ArH); ^{13}C RMN (75 MHz, $CDCl_3$): δ_C 60.8 (*C*HCN), 68.2 (*C*H_2CH), 73.7 (*C*H_2OPh), 115.3 (CN), 127.8, 127.9, 128.1, 128.5, 128.6, 130.0, 134.1, 136.7 (ArC), 164.5 (CO); MS (EI): *m/z* 281 (M^+, 0.4%), 174 (10), 106 (37), 105 (75), 91 (100), 77 (37); HRMS calcd for $C_{17}H_{15}O_3N$: 281.1052, found: 281.1063; HPLC: DAICEL CHIRACEL OD-H, λ = 254 nm, *n*-hexane/2-propanol, 97/3, 1 mL/min, t_r= 23.3 and **25.1** min.

4.2.15. (*R*)-2-(4-Methoxybenzoyloxy)-2-phenylacetonitrile 4a'. Colorless oil; $[\alpha]^{25}_D$= +12.1 (*c* 1.0, $CHCl_3$) (55% *ee*); TLC: R_f 0.70 (n-hexane/ethyl acetate, 3/2); IR (neat): ν_{max} 2225, 1734, 1258, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.87 (s, 3H, OCH3), 6.66 (s, 1H, CHCN), 6.93 (d, J = 8.9 Hz, 2H, ArH), 7.47 (m, 3H, ArH), 7.60 (m, 2H, ArH), 8.02 (d, J = 8.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.5 (CH3), 63.0 (CHCN), 114.0 (ArC), 116.4 (CN), 113.9, 120.3, 127.8, 129.2, 130.3, 132.1, 161.4 (ArC), 164.3 (CO); MS (EI): m/z 267 (M^+, 7%), 135 (100), 116 (32); HRMS calcd for $C_{16}H_{13}NO_3$: 267.0895; found: 267.0886; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, n-hexane/2-propanol, 98/2, 1 mL/min, t_r = 22.2 and **24.8** min.

4.2.16. (*R*)-2-(4-Chlorobenzoyloxy)-2-phenylacetonitrile 4a''. White powdered solid; mp 143-144 ºC (from n-hexane/ethyl acetate); $[\alpha]^{25}_D$= +6.9 (*c* 1.0, $CHCl_3$) (58% *ee*); TLC: R_f 0.76 (n-hexane/ethyl acetate, 3/2); IR ($CHCl_3$): ν_{max} 2334, 1735, 1254 and 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.66 (s, 1H, CHCN), 7.46 (m, 5H, ArH), 7.59 (m, 2H, ArH), 7.94 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 63.5 (CHCN), 116.0 (CN), 127.8, 128.0, 129.1, 129.3, 129.4, 130.5, 131.5, 141.4 (ArC), 163.8 (CO); MS (EI): m/z 271 (M^+ 29%), 141 (33), 139 (100), 116 (70), 105 (27); HRMS calcd for $C_{15}H_{10}ClNO_2$: 271.0400; found: 271.0400; HPLC: DAICEL CHIRALPAK AD, λ = 254 nm, n-hexane/2-propanol, 99/1, 0.7 mL/min, t_r = **24.6** and 26.8 min.

4.3. NLE studies for the cyanobenzoylation of benzaldehyde catalyzed by 1:1 BINOLAM:Ti(OiPr)4

The general procedure illustrated above for the cyanobenzoylation of benzaldehyde was followed. Four experiments were carried using a) racemic BINOLAM; b) partially enriched (*S*)-BINOLAM (33% *ee*); c) partially enriched (*S*)-BINOLAM (66% *ee*); d) (*S*)-BINOLAM (99% *ee*). After the usual work-up the crude material **4a** was examined by HPLC as shown in the general procedure. The following results for **4a** were obtained: a) 0% *ee*; b) 18% *ee*; c) 35% *ee*; d) 68% *ee*.

4.4. Computational details

For the computational work we used a closed-shell DFT (B3LYP) treatment,[26] as implemented in the Gaussian 03 package,[27] with the 6-31G* basis set for all atoms.[28] The original input structures were the optimized structures resulting from prior semiempirical work (not shown) carried out with PM3 as implemented in the Spartan package.[29] Electron correlation was incorporated, in part, to our studies by means of density functional theory (DFT),[30] by using the non-local hybrid three-parameter functional developed by Becke and denoted B3LYP exchange-correlation functional.[31,32] It must be emphasized that optimizations have been carried out with keywords for tight convergence criteria as well as for using the ultrafine integration grid of the program. Vibrational analysis was applied to all B3LYP/6-31G* stationary points by diagonalization of their Hessian matrices (vibrational analysis).[33] Ground state equilibrium geometries on the potential energy surface were recognized as having real frequencies only, whereas transition structures were recognized as having only one negative eigenvalue (visualized with the help of an appropriate application). Unless otherwise noted only electronic energies are given in the text. In all cases, the zero-point vibrational energies (ZPVE) were computed at the same level, though were not scaled. Cartesian coordinates of the stationary points found in this study are available upon request.

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References and notes

1. For reviews on enantioselective synthesis of cyanohydrins and their derivatives, see: a) Effenberger, F. *Angew. Chem. Int. Ed.* **1994**, *33*, 1555-1564; b) Gregory, R.J.H. *Chem. Rev.* **1999**, *99*, 3649-3682; c) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun*. **2002**, 1989-1999; d) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147-176; e) Brunel, J.-M.; Holmes, I.P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752-2778; f) Achard, T.R.J.; Clutterbuck, L.A.; North, M. *Synlett* **2005**, 1828-1847; g) Chen, F-X.; Feng, X. *Synlett* **2005**, 892-899; h) Chen, F-X.; Feng, X. *Current Organic Synthesis* **2006**, *3*, 77-97; i) North, M.; Usanov, D.L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146-5226; j) Holt, J.; Hanefeld, U. *Curr. Org. Synth.* **2009**, *6*, 15-37; i) Wang, W.; Liu, X.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2010**, 4751-4769.
2. For recent reviews on dual-action catalysts, see: a) Ma, J.A.; Cahard, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566-4583; b) Shibasaki, M.; Kanai M. in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), John Wiley & Sons, Hoboken, 2007, pp. 383-410; c) Takemoto, Y.; Miyabe, H. *Chimia* **2007**, *61*, 269-275; d) Grotjahn, D.B. *J. Chem. Soc. Dalton Trans.* **2008**, 6497-6508; e) Takizawa, S.; Katayama, T.; Sasai, H. *Chem. Comm.* **2008**, 4113-4122.
3. For a recent review about BINOLAMs as chiral ligands, see Nájera, C.; Sansano, J.M.; Saá, J.M. *Eur. J. Org. Chem.* **2009**, 2385-2400.
4. Casas, J.; Nájera, C.; Sansano, J.M.; Saá, J.M. *Org. Lett.* **2003**, *4*, 2589-2592.
5. Baeza, A.; Casas, J.; Nájera, C.; Sansano, J.M.; Saá, J.M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3143-3146.
6. Baeza, A.; Casas, J.; Nájera, C.; Sansano, J.M.; Saá, J.M. *Tetrahedron: Asymmetry* **2003**, *14*, 197-200.
7. a) Francis, F.; Davis, O.C.M. *J. Chem. Soc.* **1909**, *95*, 1403-1409; b) Marvel, C.S.; Brace, N.O.; Miller, F.A.; A.R. Johnson, *J. Am. Chem. Soc.* **1949**, *71*, 34-36; c) Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188-1190; d) Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679-2681.
8. Baeza, A.; Nájera, C.; Sansano, J.M.; Saá, J.M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385-2389.
9. For some relevant titanium(IV)-catalyzed cyanations, see: a) Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett*. **1987**, 2073-2076; b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515-1522; c) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969-7975; d) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233-6236; e) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412-7413; f) Belokon', Y.N.; Green, B.; Ikonnikov, N.S.; Larichev, V.S.; Lokshin, B.V.; Moscalenko, M.A.; North, M.; Orizu, C.; Peregudov, A.S.; Timofeeva, G.I. *Eur. J. Org. Chem.* **2000**, 2655-2661; h) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691-694; i) Chang, C-W.; Yang, C-T.; Hwang, C-D.; Uang, B-J. *Chem. Commun*. **2002**, 54-55; j) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 17111-17117; k) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592-11593; l) Wang, W.; Gou, S.; Liu, X.; Feng, X. *Synlett* **2007**, 2875-2878; m) Shen, K.; Liu, X.; Li, Q.; Feng, X. *Tetrahedron* **2007**, *64*, 147-153; n) Zeng, Z.; Zhao, G.; Gao, P.; Tang, H.; Chen, B.; Zhou, Z.; Tang, C. *Cat. Comm.* **2007**, *8*, 1443-1446; o) Belokon', Y.N.; Clegg, W.; Harrington, R.W.; Ishibashi, E.; Nomura, H.; North, M. *Tetrahedron* **2007**, *63*, 9724-9740; p) Zeng, B.; Zhou, X.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 5129-5136; q) Gou, S.; Chen, X.; Xiong, Y.; Feng, X. *J. Org. Chem.* **2006**, *71*, 5732-5736; r) Yoshinaga, K.; Nagata, T. *Adv. Synt. Cat.* **2009**, *351*, 1495-1498; s) Zhang, Z.; Wang, Z.; Zhang, R.; Ding, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 6746-6750.
10. For detailed mechanistic studies upon the enantioselective, titanium(IV)-catalyzed addition of dialkylzinc to aldehydes, see Walsh, P.J. *Acc. Chem. Res.* **2003**, *36*, 739-749.
11. Part 2. Accompanying paper.
12. Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059-1070.
13. a) Curtin, D.Y. *Rec. Chem. Progr.* **1954**, *15*, 111-128; b) Hammett, L.P. *Physical Organic Chemistry*, Second Edition, McGraw-Hill Book Company, **1970**. See also: c) Anslyn, E.V.; Dougherty, D.A. *Modern Physical Organic Chemistry*, University Science Books, **2006**.
14. To the best of our knowledge, metal-catalyzed acylcyanations appear to be circumscribed to titanium(IV) and vanadium catalysts. See: a) Belokon', Y.N.; Gutnov, A.V.; Moskalenko, M.A.; Yashkina, L.V.; Lesovoy, D.E.; Ikonnikov, N.S.; Larichev, V.S.; North, M. *Chem. Commun.* **2002**, 244-245; b) Belokon', Y.N.; Carta, P.; Gutnov, A.V.; Maleev, V.; Moskalenko, M.A.; Yashkina, L.V.; Ikonnikov, N.S.; Voskovoev, N.V.; Khrustalev, V.N.; North, M. *Helv. Chim. Acta* **2002**, 85, 3301-3312; c) Belokon', Y.N.; Blacker, A.J.; Clutterbuck, L.A.; North, M. *Org. Lett.* **2003**, *5*, 4505-4507; d) Belokon', Y.N.; Blacker, A.J.; Carta, P.; Clutterbuck, L.A.; North, M. *Tetrahedron* **2004**, *60*, 10433-10447; e) Yuang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763-4767; f) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592-11593; g) Belokon', Y.N.; Clegg, W.; Harrington, R.W.; Maleev, V.I.; North, M.; Pujol, M.O.; Usanov, D.L.; Young, C. *Chem. Eur. J.* **2009**, *15*, 2148-2165.
15. a) Hoffmann, H.M.R.; Ismail, Z.M.; Hollweg, R.; Zein, A.R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807-1810; b) Paurier, D.; Berthiaume, D.; Boivin R.P. *Synthesis* **1999**, 1423-1425; c) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995-6003; d) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195-6196; e) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; f) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid,P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621-631; g) Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225; h) Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320-11330; i) Li, F.; Widyan, K.; Wingstrang, E.; Moberg, C. *Eur. J. Org. Chem.* **2009**, 3917-3922; i) Wingstrang, E.; Laurell, A.; Fransson, L., Hult, K.; Moberg, C. *Chem. Eur. J.* **2009**, *15*, 12107-12113.
16. Wabnitz, T.C.; Yu, J-Q.; Spencer, J.B. *Chem. Eur. J.* **2004**, *10*, 484-493.
17. Cyanophosphorylations catalyzed by "BINOLAM-AlCl" using commercial $(EtO)_2P(O)CN$ have been shown to involve the addition of HCN. See: A. Baeza, C. Nájera, J.M. Sansano, J.M. Saá, *Chem. Eur. J.* **2005**, *11*, 3849-3862.
18. Trimethylsilylcyanations (using Me_3SiCN) of aldehydes catalyzed by "BINOLAM-AlCl" have been reported to involve the addition of HCN. See: J. Casas, C. Nájera, J.M. Sansano, J.M. Saá, *Tetrahedron* **2004**, *60*, 10487-10496.
19. Cyano alkoxycarbonylations (using MeOOCCN) of aldehydes catalyzed by "BINOLAM-AlCl" have been reported to involve the addition of HCN. See: A. Baeza, J. Casas, C. Nájera, J.M. Sansano, J.M. Saá, *Eur. J. Org. Chem.* **2006**, 1949-1958.
20. Trimethylsilylcyanations (using Me_3SiCN and an alcohol) of ketones promoted by a chiral tertiary amino-urea as organocatalyst actually involve the addition of HCN. See: S.J. Zuend, E.N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872-15883.
21. Trimethylsilylations (using Me_3SiCN) of aldehydes catalyzed by "BINOLateTiX_2" species have been proved to involve HCN. See: F. Yang, S. Wei, C-A Chen, P. Xi, L. Yang, Y. Lang, H-M. Gau, J. You, *Chem. Eur. J.* **2008**, *14*, 2223-2231.
22. Lundgren, S.; Wingstrand, E.; Moberg, C. *Adv. Synt. Cat.* **2007**, 349, 364-372.
23. Erhardt, S.; Grushin, V.V.; Kilpatrick, A.H.; Macgregor, S.A.; Marshall, W.J.; Roe,D.C. *J. Am. Chem. Soc.* **2008**, *130*, 4828-4845.
24. Other Ti-catalyzed reactions are severely dependant of the ligand to titanium(IV) ratios. See, for example: Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W-J.; Chen, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5747-5749.
25. Pentacoordinated titanium(IV) enolates Cl_4TiOR^- have been demonstrated to have diradical character. Both close-shell and open-shell wave functions have been used for their description. See, Moreira, I. de P.; Bofill, J.M.; Anglada, J.M.; Solsona, J.G.; Nebot, J.; Romea, P.; Urpí, F. *J. Am. Chem. Soc.* **2008**, *130*, 3242-3243
26. All calculations were carried out with the Gaussian03 package. Gaussian 03, Revision C.02: Frisch, M.J.; Trucks, G.W.; Schlegel,

H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A.Jr.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J.A.

27. a) Hehre, W.J.; Ditchfield, R.; Pople, J.A. *J. Chem. Phys.* **1972**, *56*, 2257-2261; b) Hariharan, P.C.; Pople, J.A. *Theor. Chim. Acta* **1973**, *28*, 213-222; c) Pietro, W.J.; Francl, M.M.; Hehre, W.J.; Defrees, D.J.; Pople, J.A.; Blinkey, J.S. *J. Am. Chem. Soc.* **1982**, *104*, 5039-5048.
28. SPARTAN, Wavefunction, Inc. Irvine, California.
29. R. G. Parr, W. Yang in *Density-Functional Theory of Atoms and Molecules*, Oxford, New York, 1989.
30. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B* **1988**, 37, 785-789.
31. a) Becke, A.D.; *J. Chem. Phys.* **1993**, *98*, 5648-5652; b) Becke, A.D. *Phys Rev. A* **1988**, *38*, 3098-3100; c) Kohn, W.; Becke, A.D.; Parr, R.G. *J. Phys. Chem.* **1996**, *100*, 12974-12980.
32. McIver, J.W.; Komornicki, A.K. *J. Am. Chem. Soc.* **1972**, *94*, 2625-2633.
33. Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4849-4852.