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

Alejandro Baeza^a, Carmen Nájera^{a,*}, José M. Sansano^{a,†}, José M. Saá^{b,‡}

^a Departamento de Química Orgánica e Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Aptdo. 99, 03080 Alicante, Spain ^b Departamento de Química, Universidad de las Islas Baleares, 07122 Palma de Mallorca, Spain

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ABSTRACT

The enantioselective titanium(IV)-catalyzed cyanobenzoylation of aldehydes using 1:1 BINOLAM/ Ti(OiPr)₄ mixtures as a precatalyst gave O-aroyl cyanohydrins **4** with good enantiomeric excesses. The standard optimization set carried out on the assumption of Curtin–Hammett behavior, led to no amelioration.

Extensive experimental and computational studies were 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 by *O*-benzoylation. Computational work carried out with mononuclear monomeric $\mathbf{M}_{\mathbf{M}}$ and dinuclear mixed dimer $\mathbf{D}_{\mathbf{IMD}}$ 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(OiPr)₄ mixtures appear to involve a reversal of the enantioselection. This, together with the fact that the benzoylation of the ligated *i*PrOH is a slow reaction, has led us to conclude that these cyanobenzoylations do not fit within the standard Curtin–Hammett kinetic scheme. Instead, such BINOLAM/Ti(OiPr)₄ – catalyzed cyanobenzoylations of aldehydes rather behave as non–Curtin–Hammett kinetic schemes. Further computational analysis is needed in order to make a clear distinction between Curtin–Hammett and non–Curtin–Hammett kinetic frameworks.

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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 In particular, 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 Me₂AlCl, and generally represented as 'BINOLAM–AlCl', work as efficient catalysts for the direct enantioselective cyanosilylations,⁴ cyanophosphorylations,⁵ and cyanoalkoxycarbonylations of aldehydes.⁶

However, most of the above cyanating reagents are moisture sensitive and, therefore, their use for large scale enantioselective cyanations should 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. However, our previously successful 'BINOLAM-AlCl' complexes were of no use for the 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 4 Å or triphenylphosphane oxide. Instead, we explored 'BINOLAM-TiX₂' complexes resulting from a 1:1 mixture of BINOLAM 1a and Ti(OiPr)₄ as catalysts for the cyanoacylation of aldehydes (3-phenylpropanal and benzaldehyde were initially employed as representative substrates). The results of this investigation have already been reported.⁸ At the time of this preliminary communication, the detailed mechanism of the action of 'BINO-LAM-TiX₂' complexes as catalysts was lacking, because the structure of titanium(IV) complexes was not well-known,9 in spite of recent advances in the field.¹⁰ Herein we fully describe the



^{*} Corresponding author. Tel./fax: +34 965903549.

E-mail addresses: cnajera@ua.es (C. Nájera), jmsansano@ua.es (J.M. Sansano), jmsaa@uib.es (J.M. Saá).

[†] Tel./fax: +34 965903549.

[‡] Tel.: +34 971173262; fax: +34 971173426.

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'BINOLAM–TiX₂' catalyzed cyanobenzoylations and illustrate some mechanistic aspects that we believe are of general validity for other catalyzed reactions. In particular, we claim that the great difficulty in optimizing some catalytic 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 'BINO-LAM–TiX₂' catalyzed cyanobenzoylations actually take place by means of an indirect process involving an enantioselective hydrocyanation, by *O*-benzoylation, which appear to behave as a non-Curtin–Hammett kinetic system.¹¹

2. Results and discussion

We previously explored some time ago the enantioselective synthesis of O-acylcyanohydrins 4 promoted by a 'BINOLAM-TiX₂' species. In particular, extensive experimentation was carried out using enantiomerically pure ligands 1–3, different titanium(IV) sources [either Ti(OiPr)₄, Ti(OiPr)₂Cl₂ or Ti(OMe)₄], different acylating reagents (acetyl cyanide, benzoyl cyanide and related aroyl cyanides), solvents (THF, toluene or CH₂Cl₂), additives (MS 4 Å, *i*PrOH, Ph₃PO), and eventual fine-tuning of the common reaction variables, as well as the ligand:titanium ratio. The best results were obtained when operating in THF at room temperature with titanium-derived catalysts prepared in situ from 1:1 BINOLAM 1a/ $Ti(OiPr)_{4}$ mixtures in the presence of arovl cvanides (incomplete conversions were observed when acetyl cyanide was employed). It is worth noting that these reactions responded to the ligandaccelerated catalysis concept as only trace amounts of the product could be observed when using Ti(OiPr)₄ (10 mol %) alone.¹² The desired O-aroyl (for the most part O-benzoyl) cyanohydrins 4 were thus obtained in good vield and with 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 of further study 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), although with some limitations. Particularly relevant is the case of α -substituted aldehydes (cyclohexanecarbaldehyde), which yielded an almost racemic product (Table 1, entry 16). Also worthy of note 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 the O-benzoylcyanohydrins **4** was determined by comparing their specific rotations with those of samples prepared by the 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).

Within the framework of a Curtin–Hammett catalytic cycle the optimization of a specific enantioselective catalytic procedure is, in general, a self-consistent adjustment of operational variables (reagents, temperature, solvent, time, additives, and so on). Initially we took for granted the Curtin–Hammett behavior of our Ti(IV)-catalyzed methodology.¹³ However, the difficulties in further improving the encouraging, although 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–TiX₂'-catalyzed cyanobenzoylation,¹¹ with the aim of understanding those mechanistic intricacies that could help us improve their efficiency and perhaps the 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 on evaluating the competing catalytic routes with the purpose of undergoing a rational, Curtin–Hammett-based optimization of 'BINOLAM–TiX₂'-catalyzed cyanobenzoylations.

2.1. Mechanistic studies: the competing catalytic routes

As illustrated in Scheme 2, four possible competing routes were considered 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 promoting the benzoylcyanation of benzaldehyde (Table 2, entry 1). Instead, we judged it probable that the observed asymmetric cyanobenzoylation of aldehydes promoted by BINOLAM/Ti(OiPr)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



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

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(OiPr)₄ mixture

Entry	R	Ar	<i>t</i> (h)	4	Yield (%) ^a /er ^b
1	Ph	Ph	6	(R)- 4a	91/84:16 ^c
2	Ph ^d	Ph	6	(S)- 4 a	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 ₆ H ₄ CH=CH	Ph	60	(R)- 4j	71/88:12
15	$n - C_6 H_{13}$	Ph	12	(R)- 4k	80/78:22 ^h
16	Cyclohexyl	Ph	8	(R)- 41	83/56:44
17	PhCH ₂ CH ₂	Ph	3	(R)- 4m	93/83:17 ^f
18	PhCH ₂ OCH 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).

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Scheme 2. Plausible catalytic routes for the BINOLAM/Ti(OiPr)₄ enantioselective cyanobenzoylation of aldehydes.

O-benzoylation (route C). Alternatively, enantiomerically enriched *O*-benzoylcyanohydrins **4** could result from a dynamic kinetic resolution (route D) of racemic cyanohydrins involving 'BINOLAM–TiX₂'-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 these 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 of catalysis taking place either through an LABB type mechanism or through a titanium cyanate or isocyanate intermediate. As reported by Spencer et al., trace amounts of Brønsted acids derived from the 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 the previous work we,¹⁷⁻¹⁹ and other groups,^{20,21} reported positive proof of the presence of HCN in the solution mixtures employed for titanium-catalyzed and aluminium-catalyzed cyanosilylations (110.5 ppm in CDCl₃),¹⁸ cyanophosphorylations (112.3 ppm in CDCl₃),¹⁷ and cyanoalkoxycarbonylations (109.8 ppm in CDCl₃).¹⁹ An additional, indirect proof for the implication of HCN in the enantioselective processes catalyzed by 'BINOLAM-AlCl' is the dramatic loss of ee when the reactions were carried out in the presence of an exogenous base, such as Et₃N, 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 .

On the other hand, the direct cyanobenzoylation (route B) is generally assumed to involve a highly reactive chiral, *N*-acylium

Table 2

Optimization of the reaction conditions for cyanoaroylation of aldehydes RCHO with aroyl cyanides catalyzed by 1:1 BINOLAM/ $Ti(OiPr)_4$ mixtures

Entry ^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(OiPr) ₄ /THF/ 24 h	(<5 ^d)/
3	Ph	1a/none/Ti(OiPr)4/THF/5 h	(>95)/84:16
4	$Ph(CH_2)_2$	1a/none/Ti(OiPr)4/THF/5 h	(>95)/83:15
5	Ph	1a/iPrOH(10 mol %)/Ti(OiPr) ₄ /THF/7 h	(>70)/64:36
6	Ph	1a/none/Ti(OiPr)4/THF/45 h	(50 ^e)/84:16
7	Ph	1a/none/TiCl ₂ (OiPr) ₂ /CH ₂ Cl ₂ /48 h	(0)/
8	Ph	Binol/none/Ti(OiPr)4/THF/72 h	(0)/
9	Ph	1a/Et ₃ N(10 mol %)/Ti(OiPr) ₄ /THF/5 h	(>95)/63:37
10	Ph	1a/Et ₃ N(50 mol %)/Ti(OiPr) ₄ /THF/5 h	(>95)/54:46
11	Ph	1a/Et ₃ N(100 mol %)/Ti(OiPr) ₄ /THF/	(>95)/50:50
		45 min	

^a The general procedure for the cyanoaroylation of aldehydes involved the treatment of a THF(dry) solution of aldehyde, at room temperature, under argon, with 3 equiv of aroyl cyanide in the presence of 10 mol % of Ti(OiPr)₄ and 10 mol % of (R)- or (S)-BINOLAM **1a**.

^b Crude yields of *O*-aroyl cyanohydrins were determined by ¹H NMR spectroscopy.

^c Determined by HPLC using chiral columns (Daicel, Chiralpack AS).

^d 10 mol % of Ti(OiPr)₄

e iPrOH was removed under vacuum.



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

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, H₂O, etc.) available either on the catalyst, or in the reaction media. The main support for this proposal was the lack of incorporation of ¹³C when H¹³CN 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 H¹³CN carefully prepared from K¹³CN and 85% H₃PO₄ and eventually distilled under extremely careful conditions is in fact a solution of H¹³CN in water in a 1:2 molar ratio.²³ Under these conditions our catalytic reaction would be guenched, thus leading to meaningless conclusions.

With this in mind, we decided to look first for the direct detection of HCN in 'BINOLAM–TiX₂'-catalyzed benzoylcyanation reactions under the experimental conditions of the operation. Pro-

vided that 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, aimed at identifying the actual mechanism of our cyanobenzoylations.

In fact, the ¹³C NMR spectrum of the solution mixture employed for cyanobenzoylations [i.e., a 1:1 mixture of BINOLAM and Ti(OiPr)₄ in the presence of an equivalent amount of commercial benzoyl cyanide] in deuterated chloroform showed a very small signal at 111.8 ppm, which was shown to correspond to HCN (as expected, a somewhat larger signal was observed when CD₃CN was used as solvent, as this solvent is usually contaminated with water). Since commercial benzoyl cyanide does not contain dissolved HCN according to ¹³C NMR measurements, the above observation must be the consequence of the reaction of iPrOH (either free or ligated to titanium) with benzovlcvanide. The O-benzovlcvanides 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 iPrOH prior to addition of benzoyl cyanide, we found the reaction to be inefficient (50% yield) even after 45 h reaction time (Table 2, entry 6). Moreover, attempted cyanobenzoylations carried out with a 1:1 BINOLAM/Ti(OiPr)₂Cl₂ mixture ended up with no reaction taking place (Table 2, entry 7), a result consistent with the irreversible protonation of the amino groups by the HCl produced during complexation. It thus became inevitable to consider the likely implication of HCN in the above 'BINOLAM-TiX₂'-catalyzed cyanobenzoylation reactions, a scenario in which the amino arms of our 'BINOLAM-TiX₂' catalyst ought to play a relevant role.

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; no reaction was 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(OiPr)₄ mixture employed for the cyanobenzoylation of aldehydes gave rise to a significant lowering of the er value. The addition of 0, 10, 50 or 100 mol % of Et₃N, 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 decrease in 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 % Et₃N (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(OiPr)₄:benzoyl cyanide, at room temperature. Our conclusion from this first set of experiments was simple: there was no observable interaction between BINOLAM and benzoyl cyanide, as revealed by a ¹H 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 aforementioned, when Ti(OiPr)₄ was added to this mixture, we immediately noticed the formation of a very small amount of HCN (broad

Table 3

Evaluation of dire	ct (route B) vs	. indirect cyano	benzoylation (r	oute C) by I	OFT (B3LYP/	6-31G [*]) calculations.
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Entry	Reactants	Relative energies in kcal/mol and absolute energies in hartrees (<i>in italics</i>)
1	M_{IMD} PhCO·CN-ts _{Si} + Biphelam + 2PhCOO <i>i</i> Pr + 2HCN	+10.04-6637,273770
2	2Biphelam + 2Ti(OiPr) ₄ + 3PhCOCN + CH ₃ CHO	0-6637,289775
3	MIMD-ts _{si} + Biphelam + 2PhCOOiPr + HCN + COCN	-14.39-6637,312699
4	$\mathbf{M}_{\mathbf{M}}$ -ts _{Si} + 8.2(<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-20.91 - 6637, 323097

Table 4 Dependence of benzoylcyanation enantioselectivity upon BINOLAM/Ti(OiPr)₄ ratios

BINOLAM/ Ti(O <i>i</i> Pr) ₄ ratio	Reaction time (h)	Conversion (%)	er	Configuration of major enantiomer of 6a
1:1	5	95	84:16	(<i>R</i>)
1:2	6	98	69:31	(R)
1:3	5	90	48:52	(R)
1:5	7	90	42:58	(S)

peak centred at 111.8 ppm) and of isopropyl benzoate (relevant signals appearing at 21.0, 68.0, 175.8 ppm) in the ¹³C 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(OiPr)₄ mixture slowly react with benzoyl cyanide, thereby giving rise to the actual catalysts and HCN. As expected, the reaction of a 1:1 BINOLAM/Ti(OiPr)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 $\mathbf{M}_{\mathbf{M}}$ and dinuclear $\mathbf{D}_{\mathbf{MD}}$ Ti(IV) complexes, as illustrated in Scheme 3. The absence of non-linear effects in the cyanobenzoylations carried



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

out with 1:1 BINOLAM/Ti(OiPr)₄ mixtures (see Experimental) indicate that only mononuclear monomeric M_M and dinuclear mixed dimers \mathbf{D}_{MD} can actually intervene as catalysts. Accordingly, we chose mononuclear titanium derivative M_M.2iPrOH and D_{IMD} .2iPrOH for this computational test.¹¹ Ion pair M_M COPh⁺NC⁻ (resulting from the reaction of M_M·2*i*PrOH with 3 equiv of PhCOCN) and the corresponding aldehyde complex M_M COPh⁺NC⁻·CH₃CHO were found to be stationary points at the B3LYP/6-31G* level of calculation. However, 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 also explored the dinuclear mixed dimer D_{IMD} as a catalyst for the direct benzoylcyanation reactions (route B). Eventually, we found the transition structure for the direct benzoylcyanation, namely **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 M_{M} -ts (relevant energy data are given in Table 3). We can thus conclude that the most favorable route for the enantioselective 'BINOLAM-TiX2' catalyzed cyanobenzoylations should be that of the indirect process (route C), which requires the intervention of an enantioselective hydrocyanation by means of HCN followed by an stereochemically inert O-benzoylation.

Since, as shown above, HCN is generated in situ by the reaction of the aroyl cyanide with *i*PrOH (either free or ligated), and most importantly, 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 be taking 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 derived 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, and so on.¹¹

It was thus of major importance to find out whether or not these Ti(IV)-catalyzed cyanobenzoylations could be definitely categorized as Curtin-Hammett or non-Curtin-Hammett kinetic systems. A straightforward comparative analysis (Table 4) of the cyanobenzoylations carried out with 1:1 BINOLAM/Ti(OiPr)₄ mixtures,⁸ with those employing 1:2 or 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(OiPr)₄ ratios as illustrated in the HPLC chromatograms provided in Figure 1. One can expect some erosion of enantioselectivity by the background reaction that takes place when using excess Ti(OiPr)₄, but definitely not a reversal of enantioselectivity. In fact, only trace amounts (<5%) of racemic O-benzoylcyanohydrin 4a were obtained when benzaldehyde was submitted to benzoylcyanation in the presence of 10 mol % ar $Ti(OiPr)_4$ (Table 2, entry 2) as the sole catalyst. We therefore conclude that at the very least, two competitive routes with opposite enantioselectivities operate in our cyanobenzoylations. With the final objective of finding the appropriate conditions for an efficient enantioselective cyanobenzoylation, we considered it 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 carry out a detailed computational study as the most reliable plan to reach our goal.¹¹

3. Conclusion

The exploration of the enantioselective benzovlcvanation of aldehvdes using less reactive cvanide derivatives such as arovl cvanides, catalyzed by BINOLAM/Ti(OiPr)4 mixtures, turned out to be difficult because the optimization armory employed on the assumption of a Curtin-Hammett kinetic framework, did not work properly. We thus planned to carry out a mechanistic study. Amongst 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 the experimental results. A short term computational analysis carried out upon mononuclear M_M and dinuclear D_{IMD} 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(OiPr)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(OiPr)₄ ratios led us to observe a reversal of enantioselection. This, together with the fact that the benzoylation of ligated iPrOH is a slow reaction, has led us to conclude that our cvanobenzovlations might not fit within the classical Curtin-Hammett kinetic scheme. We plan to carry out 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 solid reagents to the reaction vessel. Anhydrous solvents were freshly distilled under an 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. IR spectra 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 the 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 the 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 70 eV 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 μ L) was added, and 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 μ L) were then added. The reaction was monitored by ¹H NMR or GC. When it was judged complete, HCl 2 M (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 MgSO₄, evaporated under vacuum, and the remaining crude material was purified by flash chromatography to yield pure benzoyl-Ocyanohydrin 4 in yields reported in the main text and Table 1. The aqueous layer was treated with a 1 M NH₃/1 M NH₄Cl buffer solution and then extracted with ethyl acetate (2×10 mL). The organic layers were dried (MgSO₄) and after filtration evaporated under vacuum to yield (S)-BINOLAM in 96% (11 mg). When using pmethoxybenzoyl cyanide and p-chlorobenzoyl cyanide, under otherwise identical conditions, compounds 4a' and 4a" were obtained. The enantiomeric 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; $[\alpha]_D^{25} = +7.7 (c 2.0, CHCl_3) (68\% ee)$; TLC: $R_f 0.51 (n-hexane/ethyl acetate, 4:1)$; IR (neat): v_{max} 2343, 1731, 1246, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl_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); ¹³C NMR (75 MHz, CHCl³): 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 C₁₅H₁₂NO₂: 237.0790, found: 237.0800; HPLC: DAICEL CHIRALPAK AS, $\lambda = 254$ 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; $[\alpha]_D^{25} = +10.9$ (*c* 1.0, CHCl₃) (56% ee); TLC: R_f 0.67 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2351, 1731, 1246, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H 3.84 (s, 3H, OCH3), 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); ¹³C NMR (75 MHz): δ_C 55.4 (CH3), 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 C₁₆H₁₃NO₂: 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; $[\alpha]_D^{25} = +9.6$ (*c* 1.0, CHCl₃) (58% ee); TLC: R_f 0.45 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2346, 1732, 1257 and 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C 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 C₁₅H₁₀ClNO₂: 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; $[\alpha]_D^{25} = +17.5$ (*c* 1.5, CHCl₃) (66% ee); TLC: R_f 0.47 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2245, 1733, 1247, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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* = *J* = 7.5 Hz, 1H, ArH), 8.06 (d, *J* = 7.8 Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₁H₁₅O₃N: 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; $[\alpha]_{25}^{25} = +2.9$ (*c* 1.0, CHCl₃) (55% ee); TLC: *R*_f 0.39 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2339, 1731, 1255, 1085, 1600, 1585, 1496, 1452, 1315, 1026 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta_{\rm H}$ 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); ¹³C NMR (75 MHz, CDCl₃): $\delta_{\rm C}$ 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 C₁₃H₉NO₃: 227.0582, found: 227.0588; HPLC: DAICEL CHIRALPAK AS, λ = 254 nm, *n*-hexane/2-propanol, 99:1, 1 mL/min, *t*_r = 12.3 and 14.7 min.

4.2.6. (R)-2-(Benzoyloxy)-2-(3-pyridyl)acetonitrile 4f

White powdered solid; m p: 66 °C (from *n*-hexane/ethyl acetate); TLC: R_f 0.31 (*n*-hexane/ethyl acetate, 3:2); IR (KBr): v_{max} 2244, 1724, 1258, 1091, 1600 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₄H₁₀N₂O₂: C, 70.6; H, 4.2; N, 11.8. Found: C, 70.3; H, 4.3; 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; $[\alpha]_D^{25} = -4.5 (c 1.3, CHCl_3) (65\% ee); TLC: R_f 0.55 (n-hexane/ethyl acetate, 4:1); IR (neat): <math>v_{max}$ 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, CH3CH=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); ¹³C 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 C₁₂H₁₁NO₂: 201.0790, found: 201.0790; HPLC: DAICEL CHIRALPAK AS, $\lambda = 254$ 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

Colorless oil; $[\alpha]_D^{25} = -4.3$ (*c* 0.5, CHCl₃) (68% ee); TLC: R_f 0.65 (*n*-hexane/ethyl acetate, 4:1); IR (neat): $v_{max}v_{max}$ 2339, 1732, 1258, 1089, 1600 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H 0.89 (t, *J* = 6.9 Hz, 3H, CH3), 1.28–1.47 (m, 6H, 3xCH2), 2.12–2.19 (m, 2H, CH2CH=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=CHCH2), 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); ¹³C NMR (75 MHz, CDCl₃): δ_C 14.0 (CH3), 22.4, 29.7, 31.3, 32.0 (CH2), 62.0 (CHCN), 115.9 (CN), 120.0 (C=CHCO), 128.1, 128.6, 130.0, 133.9 (ArC), 141.0 (CH2CH=CH), 164.6 (CO); MS (EI): *m/z* 257 (M⁺, 0.3%), 125 (7), 105 (100), 77 (18); HRMS calcd for C₁₆H₁₉NO₂: 257.1416, found: 257.1411; HPLC: DAICEL CHIRAL-CEL OJ, λ = 254 nm, *n*-hexane/2-propanol, 93:7, 1 mL/min, *t*_r = 6.5 and 7.4 min.

4.2.9. (2R,3E)-2-(Benzoyloxy)-4-phenylbut-3-enenitrile 4i

Colorless oil; $[\alpha]_D^{20} = +7.5$ (*c* 1.4, CHCl₃) (82% ee); TLC: *R*_f 0.49 (*n*-hexane/ethyl acetate, 4:1); IR (neat): *v*_{max} 2226, 1732, 1246, 1089,

1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta_{\rm H}$ 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); ¹³C NMR (75 MHz, CDCl₃): ¹³C NMR (75 MHz, CDCl₃): $\delta_{\rm C}$ 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 C₁₇H₁₃O₂N: 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-3enenitrile 4j

Colorless oil; $[\alpha]_D^{25} = +3.9 (c 1.0, CHCl_3) (76\% ee)$; TLC: $R_f 0.46 (n-hexane/ethyl acetate, 4:1)$; IR (neat): v_{max} 2238, 1730, 1606, 1252, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl_3): δ_H 3.83 (s, 3H, OCH3), 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, 2H, ArH), 7.48 (t, J = 7.8 Hz, 2H, ArH), 7.63 (t, J = 7.8 Hz, 1H, ArH), 8.07 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl_3): δ_C 55.3 (CH₃), 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 C₁₈H₁₅O₃N: 293.1052, found: 293.1075; HPLC: DAICEL CHIRALPAK AS, $\lambda = 260$ 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

Colorless oil; $[\alpha]_D^{25} = +10.1$ (*c* 0.7, CHCl₃) (58% ee); TLC: R_f 0.29 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2345, 1739, 1266, 1093 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H 0.90 (t, *J* = 6.7 Hz, 3H, CH₃), 1.26–1.45 (m, 6H, $3 \times CH_2$), 1.53–1.63 (m, 2H, CH₂), 2.04 (dd, *J* = 15.6, 6.7 Hz, 2H, CH2CH), 5.58 (t, *J* = 6.7 Hz, 1H, CH0), 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); ¹³C NMR (75 MHz, CDCl₃): δ_C 14 (CH3), 22.4, 24.6, 28.5, 31.4, 32.4 (CH2), 61.6 (CH), 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 C₁₉H₁₄NO₂: 245.1416; found: 245.1417; CG: WCOT γ -CD (stationary phase FS-Lipodex-E, 0.25 μ m), *T*_{injector} = 250 °C, *T*_{detector} = 260 °C, *T*_{column} = 90 °C (5 min) to 180 °C (0.6 °C/min), *P* = 120 KPa, *t*_r = 152.5 and 152.9 min.

4.2.12. (R)-2-(Benzoyloxy)-2-cyclohexylacetonitrile 41

Colorless prisms; m p: 101 °C (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, CDCl₃): δ_H 1.19–1.33 (m, 6H, CH2), 1.72–2.01 (m, 5H, CH2 + CHCH2), 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₇NO₂: C, 74.1; H, 7.0; N, 5.8. Found: C, 73.8; H, 6.8; N, 5.8. HPLC: DAICEL CHIRALPAK AS, $\lambda = 254$ 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

Colorless oil; $[\alpha]_D^{25} = +13.9$ (*c* 2.0, CHCl₃) (65% ee); TLC: R_f 0.40 (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2333, 1731, 1263, 1104 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H 2.35–2.43 (m, 2H, CH2CHO), 2.93 (t, *J* = 7.6 Hz, 2H, CH2Ph), 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); ¹³C NMR (75 MHz, CDCl₃): δ_C 30.8 (CH2CHO), 33.9 (CH2Ar),

61.0 (CH), 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 C₁₇H₁₆NO₂ (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

Colorles oil; $[\alpha]_D^{25} = +10.1$ (*c* 1.0, CHCl₃) (38% ee); TLC: $R_f 0.27$ (*n*-hexane/ethyl acetate, 4:1); IR (neat): v_{max} 2247, 1732, 1262, 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ H 3.91 (d, *J* = 5.5 Hz, 2H, CH2CH), 4,66 (d, *J* = 3.0 Hz, 2H, CH2O), 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); ¹³C NMR (75 MHz, CDCl₃): δ_C 60.8 (CHCN), 68.2 (CH2CH), 73.7 (CH2OPh), 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 C₁₇H₁₅O₃N: 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; $[\alpha]_D^{25} = +12.1$ (*c* 1.0, CHCl₃) (55% ee); TLC: R_f 0.70 (*n*-hexane/ethyl acetate, 3:2); IR (neat): v_{max} 2225, 1734, 1258, 1086 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₆H₁₃NO₃: 267.0895; found: 267.0886; HPLC: DAICEL CHIR-ALPAK AS, $\lambda = 254$ 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 °C (from *n*-hexane/ethyl acetate); $[\alpha]_D^{25} = +6.9$ (*c* 1.0, CHCl₃) (58% ee); TLC: R_f 0.76 (*n*-hexane/ethyl acetate, 3:2); IR (CHCl₃): v_{max} 2334, 1735, 1254 and 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₀ClNO₂: 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*)-BINO-LAM (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 molecular skeletons 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 should be noted 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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