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Curtin-Hammett vs. non-Curtin-Hammett frameworks in optimizing the enantioselective binolam/titanium(IV)-catalyzed cyanobenzoylation of aldehydes. Part 2

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ARTICLE INFO

ABSTRACT

Article history: Extensive experimental and computational studies have been carried out upon the enantioselective titanium(IV)-catalyzed cyanobenzoylation of aldehydes using 1:n Binolam:Ti(OiPr)₄ mixtures as precatalysts, 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 cyanobenzoylation but an indirect process involving enantioselective hydrocyanation followed by *O*-benzoylation. Computational work provided positive evidences for the intervention of both indirect and direct cyanobenzoylation routes, the former being faster. However, the standard Curtin-Hammett-based optimization search ended with unsatisfactory results. Experimental and computational DFT studies (B3LYP/6-31G*) have now led us to conclude that: 1) the overall cyanobenzoylation of aldehydes catalyzed by 1:n Binolam:Ti(OiPr)₄ mixtures involves an enantioselective hydrocyanation followed by an stereochemically inert *O*-benzoylation; 2) the initial complexes prevailing in a 1:1 Binolam:Ti(OiPr)₄ mixture are the solvated mononuclear monomer **5.2**(iPrOH) and solvated dinuclear dimer **9.2**(iPrOH), whereas **9.2**(iPrOH) is the major component in a 1:2 or higher 1:n mixture; 3) since the slowest step is that of benzoylation of ligated iPrOH which yields the actual catalysts **5-9**, the catalytic system fits into a non-Curtin-Hammett framework, the final products deriving from a kinetic quench of the competing routes; 4) accordingly, catalysis by 1:1 Binolam:Ti(OiPr)₄ mixtures should involve cyanobenzoylations promoted by mononuclear **5**, contaminated with those promoted by some dinuclear open dimer **9**, whereas cyanobenzoylations catalyzed by a 1:2 and higher 1:n mixtures should be the result of catalysis promoted by large amounts of dinuclear open dimer **9**.

1. Introduction

Evidences have been provided in support of the involvement of an LABB (Lewis Acid-Brønsted Base) cooperative,¹ dual action mechanism for “Binolam-AlCl₃”-catalyzed enantioselective cyanation reactions, the overall reaction taking place through an indirect route involving hydrocyanation followed by *O*-functionalization. In these reactions, according to the reported data, the aluminium atom of the in situ-generated catalyst plays the role of a Lewis acid (LA), while the N atom acts as a Brønsted base (BB) in catching the available HCN in the mixture (either present in the commercial samples, or being generated by induced hydrolysis of the cyanide reagent employed induced by trace amounts of water contained in the molecular sieves, or otherwise).^{2,3,4,5} Unfortunately, such a detailed knowledge of the mechanism of action of the analogous “Binolam-TiX₂” catalysts is lacking, among other reasons because the structure of the titanium(IV) complexes initially formed (precatalysts), as well as ~~that of the~~ the actual catalysts, is not well-known,⁶ in spite of recent

advances in the field.⁷ In this work we will try to show that our “Binolam-TiX₂” catalyzed cyanobenzoylations are particularly difficult to optimize because these reactions do not fit within the usual Curtin-Hammett (C-H) construction.⁸ More on the contrary, as it will be shown below, “Binolam-TiX₂” catalyzed cyanobenzoylations rather behave as a non-Curtin-Hammett framework. So, let us shed light upon the C-H principle prior to analyze and discuss the results.

The basic Curtin-Hammett (C-H)/Winstein-Holness (W-H) kinetic system illustrated in Scheme 1 describes the relationship between two equilibrating molecules (or two conformations of a single molecule) and their reactivity.⁹ For our present purposes we can think of A and B as equilibrating catalysts involved in an asymmetric catalytic system.

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Scheme 1. Basic Curtin-Hammett(C-H)/Winstein-Holness(W-H) kinetic system.

Within this general kinetic scheme, three different situations need to be distinguished. For the first case, where boundary conditions k_A and $k_B \gg k_C$ and k_D apply, the equilibrium $A \rightleftharpoons B$ is maintained throughout the reaction or, to put it in other words, the ratio $[B]/[A]$ is time invariant. Both the Curtin-Hammett principle and the Winstein-Holness equation hold for the case in point, and only for it (see below). In this scenario (Scheme 2, upper profiles) the Curtin-Hammett principle establishes that the ratio of products is given by the equation $[D]/[C] = K k_D/k_C = e^{-\Delta\Delta G^\ddagger/RT}$.^{9,10} The second case is characterized by having the opposite boundary conditions, i.e. the catalytically active species A and B are separated by a large kinetic barrier, larger than those of the subsequent enantioselective reactions, i.e. k_C and $k_D \gg k_A$ and k_B (Scheme 2, lower profiles). In this instance, a kinetic quenching occurs since the equilibrium $A \rightleftharpoons B$ is stopped during the reaction; that is, A and B are quenched by the reaction in their equilibrium concentrations. For this case, the ratio of products $[D]/[C]$ will be equal to $K = k_B/k_A$ at 100% conversion, i.e. the ratio of products at infinity is equal to the ratio of starting materials at reaction initiation $[D]/[C]_\infty = [B]_0/[A]_0$.^{9,10} The third case in point, defined by boundary conditions k_A and $k_B \approx k_C$ and k_D , does not maintain the equilibrium $A \rightleftharpoons B$ throughout the reaction, thus requiring a complex kinetic treatment (not shown).^{9,10} These two later cases do not follow the Curtin-Hammett principle and thus, strictly speaking, both could be identified as non-Curtin-Hammett. As will be shown below, our titanium(IV)-catalyzed cyanobenzoylations fall within the above second category. Accordingly, for the sake of convenience, along the discussion we will refer to these second case profiles as if they were the only non-Curtin-Hammett kinetic frameworks (Scheme 2, lower profiles).

Scheme 2. Curtin-Hammett and non-Curtin-Hammett profiles for the basic C-H/W-H kinetic system.

The ligand-accelerated-catalysis principle is the key pillar of an optimization search based on a Curtin-Hammett framework,¹¹ in which fast equilibrating mixtures of catalytically active components try to reach their transition states thereby leading to products. Actually, most asymmetric catalysis involving metal complexes as catalysts behave as Curtin-Hammett kinetic systems.

There are, however, instances where the initially formed metal complexes (precatalytic mixture a, b in Scheme 3) react with the reagent employed thus giving rise to a new catalytic mixture (A, B in Scheme 3). The question arising in this case is whether or not this system behaves as a Curtin-Hammett or a non-Curtin-Hammett kinetic framework. It will certainly behave as a C-H system if the barrier for the conversion of a,b into A,B is low compared to $\Delta G_C^\ddagger$ and $\Delta G_D^\ddagger$ as in the standard C-H construct (Scheme 2, upper profiles). However, if the formation of the catalytic mixture A,B from equilibrating precatalysts a,b were to involve a high energy barrier, then the newly formed catalysts A and B will have no time to interconvert because k_C and $k_D \gg k_A$ and k_B , in which case one could reach a non-Curtin-Hammett-like behaviour (Scheme 3). Such systems have been described by Seeman as kinetic systems with “feed-in” mechanisms.¹⁰ Though the exact analytical solution of the system kinetics is complex, it can be easily assessed that a kinetic quench will also take place in this case provided that $k_A \approx k_B$,¹² the consequence being that each catalytic route ($A \rightarrow C$, $B \rightarrow D$) will contribute to the final products according to the relative proportions of precatalysts a and b. In other words, for this particular case, as for the standard non-Curtin-Hammett system studied above (Scheme 2, lower profiles), for the present case the ratio of products $[D]/[C]$ will also be equal to $K = k_B/k_A = [b]_0/[a]_0$ at 100% conversion. Accordingly, we will refer to this “feed-in” mechanism as a non-Curtin-Hammett-like system, also. Most interesting, the present theoretical study shows that “Binolam-TiX₂” catalyzed benzoylcyanations actually evolve through a “feed-in” mechanism and so behave as a non-Curtin-Hammett system.

Scheme 3. “Feed-in” mechanism behaving as a non-Curtin-Hammett kinetic system.

The corollary is obvious: before starting an optimization search one should be sure that his/her system is under the umbrella of a Curtin-Hammett framework, in which case the adventure of optimizing a specific enantioselective catalytic procedure is, in general, a self-consistent adjustment of operational variables (temperature, solvent, concentration of reagents, time, etc). On the contrary, a non-Curtin-Hammett or non-Curtin-Hammett-like mechanism, characterized by a kinetic quench of the active catalytic routes, may be quite hard to optimize (optimization may require the modification of structural variables namely ligand modification, change of metal derivative, etc) because in this case product formation depends on the relative amounts of the catalytically active components, only.

Some time ago we reported preliminary results on the search for an enantioselective protocol for the direct cyanoacylation of aldehydes. The standard adjustment of operational variables led us to a protocol that called for the preparation, at room temperature, of a 1:1 mixture of (*S*)-Binolam **3a** and Ti(OiPr)₄ in anhydrous THF followed, without removal of *i*PrOH, by

treatment with commercial benzoyl cyanide **2** and the appropriate aldehyde **1** (Scheme 4). A number of (*R*)-*O*-benzoylcyanohydrins **4** were actually obtained by working under these conditions,¹³ their enantiomeric ratios ranging from 60:40 to 84:16.¹⁴ Further attempts to improve these results, carried out on the assumption that we were under C-H conditions, led however to no amelioration (see below).¹⁵

Scheme 4. Catalytic system employed for the enantioselective cyanobenzoylation of aldehydes.

These difficulties in further improving the encouraging, though nevertheless insuperable, (84:16) enantiomeric ratio drove us to carry out both extensive experimental and computational studies upon the “Binolam-TiX₂” catalyzed cyanobenzoylation, with the aim of learning on those mechanistic intricacies that could eventually help us in improving its efficiency, and perhaps that of related reactions as well.¹⁶ In particular, we were worried by the possibility that the initially formed titanium(IV) complexes (presumably the catalytically active species for a direct cyanobenzoylation) could react with the reagent employed, namely benzoyl cyanide, thus giving rise to HCN that could promote instead an indirect cyanobenzoylation involving enantioselective hydrocyanation followed by *O*-benzoylation.¹⁷ If this reaction of the initially-formed complexes with benzoyl cyanide were to occur at a rate much slower than that of the actual hydrocyanation (if $k_A, k_B \ll k_C, k_D$), then a non-Curtin-Hammett scheme might be operative (Scheme 3). In fact, as will be shown below, “Binolam-TiX₂” catalyzed cyanobenzoylations operate within a non-Curtin-Hammett-like framework and, therefore, they are extremely difficult to optimize. Apart of the specific significance that this result has for our future work with Ti(IV) cyanobenzoylations, we believe that the present study is of general interest for researchers involved in asymmetric catalysis.

Thus, for a non-Curtin-Hammett kinetic system it is of major importance to know which are the precatalytic (a,b,...), and catalytic species (A,B,...). A perusal of the literature shows that enantioselective catalysis promoted by 1,2-diol and Binol-titanium(IV) complexes,^{18,19} usually represented in an imprecise manner as (DIOLate)TiX₂ and (BINOLate)TiX₂ species, are notorious in giving hard times to those involved in optimizing a promising procedure to a reliable experimental protocol, the difficulties usually being ascribed to the fluxionality and kinetic lability of titanium(IV) oxocomplexes.²⁰ The lability of such complexes can be traced down to titanium(IV) oxophilycity, itself responsible of the tendency of titanium complexes to form homo or hetero aggregates, as well as of titanium reactivity towards oxygen donors such as water or alcohols,^{21,22} not underscoring the capacity of titanium complexes to undergo inter or intramolecular rearrangements.²³ Accordingly, among the additional operational variables which need to be controlled at the optimization step of a titanium(IV)-catalyzed procedure, stoichiometry is a major factor to be adjusted,^{24,25} as well as the

presence of poisons or activators,^{26,27} either chiral,²⁸ or achiral.²⁹ Moreover, other apparently trivial matters such as the order of addition of reactants,³⁰ the aging of the precatalytic mixture,³¹ as well as other procedural issues such as the presence or absence of molecular sieves,³² or even their drying procedure,³³ quite often affect the efficiency of titanium(IV)-catalyzed enantioselective chemistry.

Conscious of the complexity of titanium alkoxide coordination chemistry,²⁰ it is therefore quite common that authors describe their active diol or Binol-titanium(IV) catalysts as precatalytic species of undetermined structure. In fact, apart of the Sharpless asymmetric epoxidation, for which extensive kinetic data has been obtained,³⁴ very few reactions are known in such mechanistic detail that one can precisely identify the structure of the actual titanium-based catalytic species responsible for the enantioselective catalytic action.³⁵ Curiously enough, even the crystalline complex resulting from a 1:1 Binol:Ti(OiPr)₄ mixture whose structure was determined by C. Martin to be the trimeric species [(BINOLate)Ti(OiPr)₂]₃·CHCl₃ in the solid state, was eventually found to disaggregate into dinuclear homodimer [(BINOLate)Ti(OiPr)₂]₂ in solution.³⁶ In fact, as recently claimed by Schneider et al.,³⁷ detailed mechanistic work needs to be done on the subject, in light of the fact that successful Ti catalyst preparations differ so much from reaction to reaction.

Efforts carried out in recent years have provided a well-defined picture of the actual titanium complexes (both in the solid state and in solution) resulting from the interaction of Binol and related ligands with titanium(IV) derivatives, not only in the absence of *i*PrOH and added water, but also in their presence. These studies have in fact revealed a complex equilibrium network involving mononuclear **M** and dinuclear **D** (dimers and mixed dimers resulting from aggregation phenomena) species, each of which could be responsible for catalysis. In particular, Heppert and co-workers using X-ray crystallography, cryoscopy and NMR spectroscopy,²³ reported that a 1:1 mixture of 3,3'-disubstituted Binols and Ti(OiPr)₄ gives rise, after removal of *i*PrOH by evaporation, to either monomeric, mononuclear **M_M** complexes (R₂BINOLate)Ti(OiPr)₂ (when bulky R substituents such as SiMe₂-*t*-Bu are seated at C₃ and C_{3'}), or to dinuclear dimers **D_D** [(R₂BINOLate)Ti(OiPr)₂]₂ (when R substituents at C₃ and C_{3'} are simple Me groups). On the other hand, dinuclear mixed dimers **D_{MD}** of general formula (R₂BINOLate)Ti(OiPr)₂·Ti(OiPr)₄ were found to be the major species (at low temperature) in equilibrium with C₂ symmetric, dinuclear, open mixed dimers **D_{oMD}** (R₂BINOLate)Ti₂(OiPr)₆, when 3,3'-disubstituted Binols reacted with Ti(OiPr)₄ in a 1:2 ratio followed by removal of *i*PrOH. Recently, Walsh and co-workers studied unsubstituted Binol:Ti(OiPr)₄ mixtures in a systematic manner, i.e. starting from 1:1 to 1:6 ratios, in order to clarify the preferential modes of coordination at each of these mixtures, for which purpose they confidently relayed upon X-ray crystallography.³⁸ In this case, the major species in a 1:1 mixture was recognized to be the 1:1 trinuclear trimer [(BINOLate)Ti(OiPr)₂]₃ **T_T**, whereas working with a 1:2 mixture yielded the 1:2 dinuclear mixed dimer (BINOLate)Ti(OiPr)₂·Ti(OiPr)₄ **D_{MD}** in which one naphtylate oxygen is linked to a second titanium atom. Finally, 1:6 mixtures furnished the 1:3 trinuclear mixed trimer (BINOLate)Ti(OiPr)₂·[Ti(OiPr)₄]₂ **T_{MT}** as a crystalline solid (in solution it loses one Ti(OiPr)₄ easily, thus leading to the above **D_{MD}**). In all of these cases, care was taken to remove *i*PrOH under vacuum.³⁹ For the particular case of the BINOLateTi-catalyzed enantioselective addition of dialkylzinc organometallics to aldehydes, Walsh and co-workers have concluded that the actual catalyst should be the dinuclear mixed

dimer (BINOLate)Ti(OiPr)₂.Ti(OiPr)₄ **D_{MD}**, in accordance with the absence of NLE in the catalytic reaction.⁴⁰ A quite different picture was drawn, however, from the closely related BINOLate-Ti allylation of ketones, thereby suggesting that seemingly minor issues might have a profound influence on the actual mechanism (in this case, the presence of isopropanol gives rise to a large improvement of *ee*).⁴¹ In another important study, the solution structure of the major species formed by mixing Binol and Ti(OiPr)₄ (no removal of *i*PrOH in this case), in different ratios (from 1:1 to 1:8), was examined by means of extensive NMR, DOSY and CD studies by Salvadori and co-workers. Their powerful analysis led to the conclusion that at low ratios (from 1:1 to 1:3), the dinuclear dimer [(BINOLate)Ti(OiPr)₂]₂ **D_D** was the major species in CDCl₃ solution, while at higher ratios the major species was the dinuclear mixed dimer (BINOLate)Ti(OiPr)₂.Ti(OiPr)₄ **D_{MD}**, both species being in fast equilibrium in solution.⁴² More in support of the sophistication of titanium(IV) complexation is another report by Salvadori and co-workers who established that a single titanium BINOLate species is observable by NMR in a 1:0.5:10 Binol:Ti(OiPr)₄:H₂O mixture, namely tetranuclear (BINOLate)₄Ti₄(μ-OH)₄,⁴³ an observation of relevance for the understanding of the enantioselective oxidation of sulfoxides carried out under such conditions.⁴⁴

As mentioned previously, due to the kinetic nature of enantioselective catalysis operating in a Curtin-Hammett framework, there may not be much help in knowing which one is the most abundant ground state precatalytic or catalytic species under a particular set of conditions. However, this information is highly relevant in the case we were under a non-Curtin-Hammett kinetic regime. Unfortunately, kinetic studies on titanium(IV) alkoxide catalysis are difficult to carry out due to their tendency to form aggregates. Accordingly, the only way left for a direct analysis of the competitive routes undergone by catalysts A, B, ... is the use of a faithful computational approach. As illustrated below this was the approach chosen to study our “Binolam-TiX₂” catalyzed benzoylcyanation of aldehydes.¹⁵

2. Results and discussion

2.1. Titanium(IV) complexes as derived by computation

A computational study, built upon the premises of the possible involvement of mononuclear **M** and dinuclear **D** titanium species as catalysts, was launched. As for our prior study on “Binolam-AlCl₃”-catalyzed cyanophosphorylations,² we have explored two possible mechanisms for “Binolam-TiX₂” catalyzed enantioselective cyanobenzoylations, namely the direct and the indirect processes (Scheme 5). While the former was conceived as an LALB type of catalysis, the latter was envisaged as an stepwise process occurring through an enantioselective hydrocyanation (an LABB catalysis), followed by *O*-benzoylation.

Scheme 5. Direct and indirect cyanobenzoylation routes computationally studied, where **1** is acetaldehyde (R=CH₃), and the model for (R)-Binolam **3a** is (R)-Biphelam.

In the event, we examined first the direct reaction of acetaldehyde with benzoylcyanide, catalyzed by mononuclear monomer **5** as a model for the direct route. Unfortunately, we found no computational evidence for the existence of a direct LALB mechanism.¹⁵ This result led us to focus our efforts on the so-called indirect mechanism. Specifically, we explored by computation the enantioselective, cooperative hydrocyanation routes catalyzed by mononuclear monomeric (**M_M**) and dinuclear dimeric (**D_D**) titanium species, either aggregated or mixed dimers, of the type that Heppert, Walsh and Salvadori proposed as possible catalysts, namely **D_D** and **D_{MD}**. As for the computational study of “Binolam-AlCl₃”-catalyzed cyanophosphorylations,² and lanthanum(III) salt complexes-catalyzed nitroaldol reactions,⁴⁵ in order to reduce the size of the titanium(IV) catalysts for study, we simplified somewhat the binaphthalene ligand by using the biphenyl analogue “biphelam”. In spite of this simplification, we were faced with the huge job of dealing with isopropyl groups in our catalyst models due to the fact that the experimental work carried out with a 1:1 mixture of Binolam:Ti(OMe)₄, led to racemic material, thus invalidating its use as model. The additional, undesired implication of this choice is the multiplication of the degrees of freedom. In such a situation one cannot rigorously assess that every single stationary point found is the lowest of all. It should be emphasized though that our input structures for DFT calculations were the stationary points from prior pm3 semiempirical calculations, itself derived from a molecular mechanics (MMFF) conformational search carried out with a commercial computational package (see the experimental part for details).

Scheme 6. Monomeric **M** and dimeric titanium(IV) **D** derivatives computationally evaluated as cyanobenzoylation catalysts.

With this in mind, the following species illustrated in Scheme 6 were computationally tested as cooperative, bifunctional catalysts for the enantioselective hydrocyanation of aldehydes, namely mononuclear monomer (**M_M**) **5**, dinuclear dimer (**D_D**) **6**, dinuclear angular mixed dimer (**D_{aMD}**) **7**, dinuclear linear mixed dimer (**D_{IMD}**) **8** and dinuclear open mixed dimer (**D_{oMD}**) **9**. For the sake of clarity we initially describe the individual routes, the overall profile being eventually analyzed and commented.

Firstly, we examined by means of DFT(B3LYP/6-31G*) calculations the equilibrium formation of the different mononuclear and dinuclear species starting from “biphelam” and Ti(OiPr)₄, or to put it other words we studied our precatalytic mixture. Interesting results came out from this computational

analysis as applied to 1:1 and 1:2 biphelam:Ti(OiPr)₄ mixtures. Thus, as shown in Scheme 7 and Table 1 in a precatalytic 1:1 mixture (notice that we have actually considered a 2:2 mixture so as to easily evaluate all possible titanium(IV) species), the initial complex biphelam:Ti(OiPr)₄ **10** can easily evolve into mononuclear **M** and dinuclear **D** complexes, namely the mononuclear, monomeric **M_M** complex **5.2(iPrOH)**, which was found to be, according to B3LYP/6-31G*, 18.50 kcal/mol more stable than starting materials, and the dinuclear, mixed dimeric **D_{oMD}** complexes, **9.2(iPrOH)**, and **9** itself, also found to be more stable than starting materials by 12.8 kcal/mol and 0.05 kcal/mol, respectively. The driving force for complexation in **5.2(iPrOH)** and **9.2(iPrOH)** is not only that corresponding to the formation of two binaphtolate-titanium (O-Ti) bonds, but also the consequence of the coordination of two *i*PrOH units to titanium (Ti-OH = 2.12-2.17 Å for the case of **5**, and 2.26-2.30 Å for the case of **9**) thereby reaching hexacoordination and, last but not least, to hydrogen bonding of the acidified OHs with the nearby nitrogen atoms pertaining to the ligand's dimethylaminomethyl arms (N-HO = 1.73-1.81 Å for the case of **5**, and 1.72-1.74 Å for the case of **9**). Accordingly, loss of these *i*PrOH molecules is quite energy costly, as revealed by the fact that **5** + 2*i*PrOH lies 26.0 kcal/mol higher in energy than **5.2(iPrOH)**, though less strongly bound *i*PrOH is apparent in **9.2(iPrOH)** which requires 12.7 kcal/mol to be desolvated. The computed energies of the solvated and desolvated dinuclear dimer (**D_D**) **6**, the dinuclear angular mixed dimer (**D_{aMD}**) **7**, and the dinuclear linear mixed dimer (**D_{lMD}**) **8** were found to lie higher than that of starting materials (Table 1). In particular, notice the exceedingly large cost of desolvation for the case of **6**. Absolute and relative energies for the stationary points of the species in biphelam:Ti(OiPr)₄ mixtures in 1:1 and 1:2 ratios are given in Tables 1 and 2. According to these data, we can conclude that: 1) only the fully solvated, mononuclear **5.2(iPrOH)**, as well as dinuclear **9**, either solvated or unsolvated,

should likely be observable species (ΔG values are needed for a definitive assessment) as they are more stable than starting materials; 2) as it can be easily recognized from the data given in Table 1, only trace amounts of free *i*PrOH should exist in these 1:1 biphelam:Ti(OiPr)₄ mixtures; 3) however, the bound *i*PrOH (in both the mononuclear or dinuclear species) may be capable of reacting slowly with the incoming benzoyl cyanide, in agreement with the experimental observations. The outcome is quite revealing: the initial equilibrium mixture of precatalysts from 1:n Binolam:Ti(OiPr)₄ mixtures does not lead to catalytic species of the type "BinolamTi(OiPr)₂" and free 2-propanol, in agreement with results previously reported by Walsh et al. for closely related ligands.⁴⁶ Instead, the equilibrium mixture of precatalysts must slowly react with benzoyl cyanide thus irreversibly giving rise to the actual catalysts **5**, **6**, **7**, **8**, **9**, isopropyl benzoate and HCN, in line with our own experimental observations.¹⁵ As a consequence of the high energy barrier of this benzoylation, the resulting mixture of titanium(IV) catalysts could then compete independently in catalyzing hydrocyanations in a non-Curtin-Hammett-like framework (Scheme 4).¹²

Table 2. Absolute and relative energies (B3LYP/6-31G*) of solvated mononuclear monomer **5**, angular mixed dimer **7**, linear mixed dimer **8** and open mixed dimer **9** complexes resulting from a 1:2 mixture of biphelam (1 equiv) and Ti(OiPr)₄ (2 equiv).

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	7.2(iPrOH)	-4209.718649	+4.88
2	8.2(iPrOH)	-4209.724566	+1.16
3	1(biphelam) + 2[Ti(OiPr) ₄]	-4209.726420	0
4	5.2(iPrOH) + Ti(OiPr) ₄	-4209.741158	-9.25
5	9.2(iPrOH)	-4209.746832	-12.81

Table 1. Absolute and relative energies (B3LYP/6-31G*) of solvated and desolvated mononuclear monomer **5**, dinuclear dimer **6**, angular mixed dimer **7**, linear mixed dimer **8** and open mixed dimer **9** complexes resulting from a 1:1 mixture of biphelam (2 equiv) and Ti(OiPr)₄ (2 equiv).

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	6 + 4(<i>i</i> PrOH)	-5169.9385811	+60.26
2	6.2(iPrOH) + 2(<i>i</i> PrOH)	-5169.987957	+29.28
3	8 + 2(<i>i</i> PrOH) + biphelam	-5170.012065	+14.15
4	7 + 2(<i>i</i> PrOH) + biphelam	-5170.015039	+12.28
5	5 + 2(<i>i</i> PrOH) + 8.2(iPrOH)	-5170.022628	+7.52
6	7.2(iPrOH) + biphelam	-5170.0268401	+3.71
7	8.2(iPrOH) + biphelam	-5170.032756	+1.16
8	2(biphelam) + 2[Ti(OiPr) ₄]	-5170.034611	0
9	9 + 2(<i>i</i> PrOH) + biphelam	-5170.034686	-0.05
10	10 + biphelam + Ti(OiPr) ₄	-5170.055023	-6.48
11	9.2(iPrOH) + biphelam	-5170.055261	-12.81
12	2 x 5.2(iPrOH)	-5170.064086	-18.50

Scheme 7. Complexation scheme of biphelam with $\text{Ti}(\text{O}i\text{Pr})_4$ leading to monomeric **M** and dimeric titanium(IV) **D** precatalysts and catalysts.

The idealistic approach called for determining the barriers for benzoylation of the ligated $i\text{PrOH}$ present in each and every complex (precatalyst). Unfortunately, this was an impracticable job due to the immense computational resources required. So we have adopted a reasonable assumption, namely that there would be not significant kinetic preference for benzoylation of the ligated 2-propanol present in any solvated complex (precatalyst). Accordingly, the barrier of benzoylation was calculated for only one complex. If, as expected, this were a large energy barrier, then it could be safely assessed which major catalysts would be

present in the reaction mixture after benzoylation. The relative energies of the species resulting from treatment of a 1:1 mixture of biphelam and $\text{Ti}(i\text{OPr})_4$ given in Table 3 show that mononuclear monomer **5** and the dinuclear, open mixed dimer **9**, are the major species together with minor amounts of the dinuclear angular and linear mixed dimers **7** and **8**, respectively. Only trace amounts, if any, of dinuclear dimer **6** should be formed. It is worth mentioning at this point that due to the mononuclear and dinuclear nature of the major catalysts **5** and **9**, the relative amounts of **5** and **9** resulting from treatment of a 1:2 (Table 4), or higher (not shown), mixtures of biphelam and $\text{Ti}(i\text{OPr})_4$ are reversed, as discussed later on. The relevant conclusion coming out from this analysis is that while in a Curtin-Hammett framework the possible role of dinuclear dimer **6** as catalyst should not be discarded, the opposite is true for a non-Curtin-Hammett or non-Curtin-Hammett-like framework, therefore being safe to assume that **6** will not be involved in cyanobenzoylation of aldehydes catalyzed either by 1:1 or 1:n Binolam: $\text{Ti}(\text{O}i\text{Pr})$ mixtures, provided that we were under a non-Curtin-Hammett kinetic system. For the sake of comparison, Table 3 illustrates the relative energies of those species resulting from reaction with benzoyl cyanide (2 equivalents), together with the energy barrier corresponding to the addition (tsA) step (being so high, it is irrelevant whether or not the barrier corresponding to the elimination step (tsE) is higher or lower) found for the benzoylation of the ligated $i\text{PrOH}$ in **5.2**($i\text{PrOH}$). It is worth mentioning that the position of entries 7 and 8 in Table 3 are inverted when tabulated data refers to reaction with 4 equivalents of PhCOCN as further reaction occurs with the remaining **5.2**($i\text{PrOH}$) (entries 7 and 8, Table 4). If, as assumed previously, similar barriers operate for the benzoylation of the ligated $i\text{PrOH}$ in the closely related complexes and these barriers are higher than those corresponding to hydrocyanations catalyzed by the actual catalysts **5**, **6**, **7**, **8** or **9** (see below), then we can definitely state that our operating conditions lie in a non-Curtin-Hammett-like framework. To substantiate this assert, or refute it, we next examined the individual routes for hydrocyanation.

Table 3. Absolute and relative energies (B3LYP/6-31G*) of the species resulting from treatment of a 1:1 mixture of biphelam (2 equiv) and $\text{Ti}(\text{O}i\text{Pr})_4$ (2 equiv) with PhCOCN (2 equiv).

Ent.	Reactants	Absolute energies (hartrees)	Relative energies (in kcal/mol)
1	5.2 ($i\text{PrOH}$). PhCOCN -tsA + PhCOCN + 5.2 ($i\text{PrOH}$)	-6045.577810	+45.87
2	5.2 ($i\text{PrOH}$). PhCOCN -tsE + PhCOCN + 5.2 ($i\text{PrOH}$)	Not calculated	Not calculated
3	6 + 2 $\text{PhCOO}i\text{Pr}$ + 2 HCN + 2($i\text{PrOH}$)	-6045.609520	+25.97
4	2(biphelam) + 2 $[\text{Ti}(\text{O}i\text{Pr})_4]$ + 2 PhCOCN	-6045.650901	0
5	8 + biphelam + 2 $\text{PhCOO}i\text{Pr}$ + 2 HCN	-6045.683004	-20.15
6	7 + biphelam + 2 $\text{PhCOO}i\text{Pr}$ + 2 HCN	-6045.685978	-22.01
7	5 + 5.2 ($i\text{PrOH}$) + 2 $\text{PhCOO}i\text{Pr}$ + 2 HCN	-6045.693567	-26.77
8	9 + biphelam + 2 $\text{PhCOO}i\text{Pr}$ + 2 HCN	-6045.705625	-34.34

Table 4. Absolute and relative energies (B3LYP/6-31G*) of the stationary points of the species resulting from treatment of biphelam (2 equiv) and Ti(OiPr)₄ (2 equiv) with PhCOCN (4 equiv).

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	5 .2(<i>i</i> PrOH).PhCOCN-tsE + 3PhCOCN + 5 .2(<i>i</i> PrOH)	Not calculated	Not calculated
2	5 .2(<i>i</i> PrOH).2PhCOCN-tsA + 3PhCOCN + 5 .2(<i>i</i> PrOH)	-6921.220467	+29.32
3	2(biphelam) + 2[Ti(OiPr) ₄] + 4PhCOCN	-6921.267191	0
4	6 + 4PhCOOiPr + 4HCN	-6921.280459	-9.12
5	8 + biphelam + 2PhCOOiPr + 2HCN + 2PhCOCN	-6921.299294	-20.15
6	7 + biphelam + 2PhCOOiPr + 2HCN + 2PhCOCN	-6921.302268	-22.01
7	9 + biphelam + 2PhCOOiPr + 2HCN + 2PhCOCN	-6921.321915	-34.34
8	2 x 5 + 4PhCOOiPr + 4HCN	-6921.323048	-35.05

2.2. Enantioselective catalytic routes promoted by mononuclear monomeric titanium(IV) complexes **M_M**

The resulting mononuclear (**M**) **5** and dinuclear (**D**) species **7**, **8** and **9** were studied computationally as cooperative, bifunctional catalysts for the enantioselective hydrocyanation of aldehydes. A priori, the mononuclear monomeric (**M_M**) species **5** could work as a bifunctional LABB catalyst through the so-called **M_{M-LABB}** bifunctional route. Actually, we were able to detect by computation a stable ternary complex **5**.HCN.CH₃CHO where, as for the case of the analogous aluminium derivative,¹⁵ the titanium atom acts as a Lewis acid for the incoming aldehyde, whereas a nitrogen atom functions as a Brønsted base capable of complexing HNC (the corresponding HCN complex was found to be unproductive). Unfortunately, the transition structure corresponding to attack to the *Re* face of the aldehyde (for simplicity, acetaldehyde was employed in our studies) for the **M_{M-LABB}** bifunctional route (Scheme 8) could not be found.

Apart of the so-called **M_{M-LABB}** bifunctional route we have also examined the **M_{M-TiCN}** and **M_{M-TiNC}** routes which involve ammonium cyanotitanate Ti-CN⁻ (this route turn out to be a dead end) and isocyanotitanate Ti-NC⁻ as intermediate species resulting from an intramolecular attack of cyanide or isocyanide to the nearby titanium atom while the nitrogen retains the proton.⁴⁷ These zwitterionic cyano or isocyanotitanate species are identified in the text as **5**.CNH⁺ and **5**.NCH⁺, respectively (Table 5).

Table 5. Absolute and relative (B3LYP/6-31G*) energies of the enantioselective hydrocyanation of CH₃CHO catalyzed by mononuclear monomeric **5** through the **M_{M-TiNC}** mechanism.

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	biphelam + Ti(OiPr) ₄ + 2PhCOCN + CH ₃ CHO	-3614.469325	0
2	10 + 2PhCOCN + CH ₃ CHO	-3614.479648	-6.48
3	5 .2(<i>i</i> PrOH) + 2PhCOCN + CH ₃ CHO	-3614.484062	-9.25
4	5 .HNC + HCN + 2PhCOOiPr + CH ₃ CHO	-3614.484529	-9.54

5	$5_{\text{TINC-ts}_{Si}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.487909	-11.66
6	$5_{\text{TINC-ts}_{Re}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.491321	-13.80
7	$5_{\text{HNC.CH}_3\text{CHO}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.492181	-14.34
8	$5_{\text{NC}^+\text{H}^+} + \text{HCN} + 2\text{PhCOOiPr} + \text{CH}_3\text{CHO}$	-3614.496857	-17.28
9	$5 + 2\text{HCN} + 2\text{PhCOOiPr} + \text{CH}_3\text{CHO}$	-3614.497253	-17.53
10	$5_{\text{CN}^+\text{H}^+} + \text{HCN} + 2\text{PhCOOiPr} + \text{CH}_3\text{CHO}$	-3614.499641	-19.02
11	$5_{\text{NC}^+\text{H}^+.\text{CH}_3\text{CHO}_{re}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.501677	-20.30
12	$5_{\text{HNC}} + \text{HCN} + 2\text{PhCOOiPr} + \text{CH}_3\text{CHO}$	-3614.503516	-21.46
13	$5_{\text{NC}^+\text{H}^+.\text{CH}_3\text{CHO}_{si}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.506244	-23.17
14	$5_{\text{HNC.CH}_3\text{CHO}} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.509160	-25.04
15	$5 + \text{CH}_3\text{CH}(\text{OH})\text{CN} + \text{HCN} + 2\text{PhCOOiPr}$	-3614.510119	-25.60

Scheme 8. Competitive routes available for mononuclear monomeric **8**: $\text{M}_{\text{M-LABB}}$ and $\text{M}_{\text{M-TiNC}}$.

The transition structures corresponding to the mononuclear, monomeric isocyanate route ($\text{M}_{\text{M-TiNC}}$) were found to be separated by 2.14 kcal/mol (B3LYP/6-31G*), the lowest one being the so-called $5_{\text{TINC-ts}_{Re}}$ which corresponds to cyanide attack at the *Re* face of the aldehyde (Fig 1). According to these data, the (*S*)-cyanohydrin derivative should predominate, as in fact it is found experimentally when employing a 1:1 mixture of (*R*)-Binolam and $\text{Ti}(\text{OiPr})_4$. Also, these results are in accordance with the absence of non-linear effects experimentally observed.¹⁵

Figure 1. Transition structures $5_{\text{TINC-ts}_{Re}}$ (lowest) and $5_{\text{TINC-ts}_{Si}}$ corresponding to the isocyanotitanate route ($\text{M}_{\text{M-TiNC}}$) undergone by mononuclear, monomeric **5**.

2.3. Enantioselective catalytic routes promoted by dinuclear, dimeric titanium(IV) complexes **D**_p

Although these results provided a satisfactory view of the experimentally observed enantioselectivity of cyanobenzoylations,¹⁵ there was an important issue that remained unanswered namely, the puzzling dependence of stereoselectivity with Binolam: $\text{Ti}(\text{OiPr})_4$ 1:n ratios. Since this change could not be assigned to the background reaction catalyzed by $\text{Ti}(\text{OiPr})_4$ only, we hypothesized that dinuclear complexes **D** could be involved. So, we further examined by computation the role that dinuclear angular mixed dimer (**D_{AMD}**) **7**, dinuclear linear mixed dimer (**D_{IMD}**) **8** and dinuclear open mixed dimer (**D_{oMD}**) **9** could play as catalysts for hydrocyanation. To simplify somewhat the discussion we will only refer to the competing transition structures resulting from these routes and their corresponding energies.

Table 6. Absolute and relative energies (B3LYP/6-31G*) of the enantioselective hydrocyanation of CH_3CHO promoted

by dinuclear, open mixed dimer **D_{oMD} 9** through the **D_{oMD}-TiNC** mechanism.

Entry	Reagents	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	2biphelam + 2Ti(OiPr) ₄ + 2PhCOCN + CH ₃ CHO	-6199.486630	0
2	9 _{TiNC-ts_{Si}} + bifelam + 2PhCOOiPr + HCN	-6199.512783	-16.41
3	9 _{TiNC-ts_{Re}} + bifelam + 2PhCOOiPr + HCN	-6199.513107	-16.61
4	9 _{NC-H⁺} + biphelam + 2PhCOOiPr + HCN + CH ₃ CHO	-6199.535357	-30.58
5	9 _{NC-H⁺} + biphelam + 2PhCOOiPr + HCN + CH ₃ CHO	-6199.536443	-31.26
6	9 + biphelam + 2PhCOOiPr + 2HCN + CH ₃ CHO	-6199.541354	-34.34

As illustrated in Tables 2, and 3 above, the dinuclear, open mixed dimer (**D_{oMD}**) **9** which corresponds to a 1:2 Binolam:Ti(OiPr)₄ ratio should also be present in the reaction media containing either a 1:1 or a 1:n Binolam:Ti(OiPr)₄ ratios. Thus, we first explored this candidate for catalysis. Both titanium atoms possess an open coordination site and are related by a C₂ axis of symmetry. Actually, **9** was found to be capable of reacting with HCN thereby giving rise to an ammonium (one nitrogen gets the proton) cyanotitanate and/or isocyanotitanate species analogous to those found for the mononuclear monomeric species (**M_M**) **5**. However, only the isocyanotitanate route was found to be productive, the corresponding transition structures **9**_{NC-ts_{Re}} and **9**_{NC-ts_{Si}} (Fig. 2) lying higher in energy than those derived from **M_M** **5** (Table 6). Transition structure **9**_{NC-ts_{Re}}, which corresponds to cyanide attack at the *Re* face of the aldehyde, was found to be only 0.2 kcal/mol lower in energy than **9**_{NC-ts_{Si}}. Therefore, the implementation of this route will eventually lead to an almost racemic product. This is in agreement with experimental facts observed when a 1:2 and 1:3 Binolam:Ti(OiPr)₄ precatalytic mixture is employed.¹⁵

Figure 2. Transition structures **9**_{NC-ts_{Re}} and **9**_{NC-ts_{Si}} corresponding to the isocyanotitanate route (**D_{oMD}-TiNC**) undergone by dinuclear, open mixed dimer **9**.

Analogously, the dinuclear, angular mixed dimer (**D_{aMD}**) **7**, which also corresponds to a 1:2 Binolam:Ti(OiPr)₄ ratio, was found to behave as an isocyanotitanate catalyst. Instead, the dinuclear, linear mixed dimer (**D_{lMD}**) **8** behaved as an LABB catalyst, one amino arm acting as Brønsted base while the nearest

titanium atom (the one closer to Binolam) works as Lewis acid. Both were considered potentially interesting because, in close agreement with experiment, no NLE should be observed as only one ligand is present in mixed dimeric species.¹⁵

The transition structures eventually found for the hydrocyanation process catalyzed by dinuclear, linear mixed dimer **D_{lMD}** **8** working as an LABB type catalyst, namely **8**_{LABB-ts_{Re}} and **8**_{LABB-ts_{Si}}, are illustrated in Fig 3.

Figure 3. Transition structures **8**_{LABB-ts_{Re}} and **8**_{LABB-ts_{Si}} corresponding to the LABB route (**D_{lMD}-LABB**) undergone by dinuclear linear mixed dimer **8**.

Two important conclusions result from this analysis. Firstly, as illustrated in Table 7 the energy-lowest transition structure amongst all those competing is **8**_{LABB-ts_{Si}}. Secondly and most enlightening, attack at the *Si* face of the aldehyde was now preferred over the alternative *Re* attack by 2.29 kcal/mol, in striking contrast to the above-mentioned preference for the *Re* attack predicted for the isocyanotitanate route available to mononuclear, monomeric (**M_M**) **5**. So, if reaction conditions were to facilitate the intervention of the **8**_{LABB} route, then the major *O*-benzoyl cyanohydrin enantiomer should be (*R*), in striking contrast to experiment.

Table 7. Absolute and relative (B3LYP/6-31G*) energies of enantioselective hydrocyanation of CH₃CHO promoted by **D**_{IMD} **8** and **D**_{aMD} **7** through the LALB (**D**_{IMD-LALB}) and the isocyanotitanate (**D**_{aMD-NC}) mechanisms.

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	2biphelam + 2Ti(OiPr) ₄ + 2PhCOCN + CH ₃ CHO	0	0
2	7 _{NC-ts_{Re}} + biphelam + 2PhCOOiPr + 2HCN	-0.51	-0.51
3	7 _{NC-ts_{Si}} + biphelam + 2PhCOOiPr + 2HCN	-2.48	-2.48
4	8 _{LABB-ts_{Re}} + biphelam + 2PhCOOiPr + HCN	-12.08	-12.08
5	8 _{LABB-ts_{Si}} + biphelam + 2PhCOOiPr + HCN	-14.39	-14.39
6	8 + biphelam + 2PhCOOiPr + 2HCN + CH ₃ CHO	-20.14	-20.14
7	7 + biphelam + 2PhCOOiPr + 2HCN + CH ₃ CHO	-22.01	-22.01
8	8 .HCN.RCHO + biphelam + 2PhCOOiPr + HCN	-24.18	-24.18

Instead, the dinuclear, angular mixed dimer (**D**_{aMD}) **7** was found to perform as an isocyanotitanate type of catalyst, as previously observed for mononuclear, monomeric (**M**_M) **5**. Two transition structures were found, namely **7**_{NC-ts_{Re}} and **7**_{NC-ts_{Si}} (Fig 4) separated by 1.97 kcal/mol (Table 7). However in opposition to the results found for **5**, the lowest transition structure was shown to be **7**_{NC-ts_{Si}}, which should give rise to the (*R*)-*O*-benzoyl cyanohydrin. However, the **D**_{aMD-NC} route promoted by **7** involves higher energy barriers than those corresponding to routes **M**_{M-TiNC} and **D**_{IMD-LABB} catalyzed by **5** or **8**, respectively.

Figure 4. Transition structures **7**_{NC-ts_{Re}} and **7**_{NC-ts_{Si}} corresponding to the isocyanotitanate route (**D**_{IMD-NC}) undergone by dinuclear, linear mixed dimers **7**.

As mentioned above, the role played by dinuclear dimer (**D**_D) **6** as an isocyanotitanate catalyst is likely to be irrelevant provided we were in a non-Curtin-Hammett framework. This, together with the enormous size of the species to be computed, led us to put apart the search for the transition structures corresponding to this route.

Merging together the above individual routes leads to the overall reaction profile illustrated in Scheme 9 and Table 8. In checking these data it can be concluded that, if our benzoylcyanations were catalyzed by a rapidly equilibrating mixture of catalysts **5-9**, or to put it in other words if our kinetic system behaved as a C-H system, then the (*S*)-*O*-benzoylcyanohydrins **4** should be obtained in high enantiomeric

ratio, as a consequence of the fact that **5**_{TiNC-ts_{Re}} and **5**_{TiNC-ts_{Si}} (belonging to the isocyanotitanate route undergone by mononuclear monomer **5**) are the transition structures of lowest energy. Of them, the lowest is **5**_{TiNC-ts_{Re}} (2.14 kcal/mol lower than **5**_{TiNC-ts_{Si}}) which should then give rise to (*S*)-*O*-benzoylcyanohydrins **4** in excellent *ee*. These predictions agree with experiment, as it also agrees with the fact that NLE effects are null. However, under a C-H kinetic system, these results should be independent of the Binolam:Ti(OiPr)₄ ratio, in striking contrast with experimental facts (1:2 or 1:3 Binolam:Ti(OiPr)₄ ratios lead to an almost racemic product). Therefore, it can be safely concluded that benzoylcyanations of aldehydes catalyzed by Binolam:Ti(OiPr)₄ mixtures do not behave as a Curtin-Hammett kinetic system.

Instead, the collected experimental data nicely fit within the framework of a non-Curtin Hammett-like regime. This is so because, according to calculations, the benzoylation of ligated 2-propanol is a very slow process (is the rate determining step), thus implying that our Ti(IV)-catalyzed benzoylcyanations of aldehydes Binolam:Ti(OiPr)₄ actually take place within the framework of a non-Curtin Hammett-like framework (similar to Seeman's "feed-in" mechanism), where products are the result of a kinetic quench of all the competing routes catalyzed by the available catalysts **5-9** at a given time. It must be kept in mind that the relative amounts of catalyst **5-9** should vary with the Binolam:Ti(OiPr)₄ ratios. Even though we do not know the precise amount of catalysts **5-9** for each particular case, we can nevertheless provide an approximate guess for the limiting case where the barriers for benzoylation of ligated *i*PrOH molecules are close to each other, i.e. for the limiting situation where the barriers for converting precatalysts **5.2iPrOH**, **6.2iPrOH**, **7.2iPrOH**, **8.2iPrOH** and **9.2iPrOH**, into the corresponding catalysts **5**, **6**, **7**, **8** and **9** are very similar. In this case the relative amounts of catalysts **5-9** should be almost identical to the relative amounts of precatalysts **5.2iPrOH-9.2iPrOH**. Thus, as illustrated in Table 2 above, the major catalyst available in a 1:1 Binolam:Ti(OiPr)₄ mixture should be mononuclear monomer **5**, perhaps contaminated with some **9** due to the fact that *i*PrOH appears to be somewhat loosely bound in **9.2iPrOH**.

Accordingly, one should obtain a medium-range enantiomeric ratio of the (*S*)-*O*-benzoyl cyanohydrins **4**, in full agreement with experiment.¹⁵ On the other hand, according to the relative energies for the remaining catalytic species, namely **6**, **7**, and **8**, no significant roles are expected for these catalysts in our Ti(IV)-catalyzed benzoylcyanation of aldehydes even under a non-Curtin-Hammett-like kinetic regime.

Table 8. Absolute and relative energies (B3LYP/6-31G*) at stationary points of the enantioselective hydrocyanation of CH₃CHO promoted by mononuclear (**M**) **5** and dinuclear (**D**) **6**, **7**, **8**, and **9** species resulting from a 2:2 biphelam:Ti(OiPr)₄ mixture in the presence of PhCOCN (2 equiv.).

Entry	Reactants	Absolute energies (in hartrees)	Relative energies (in kcal/mol)
1	6 + 4(<i>i</i> PrOH) + 2PhCOCN + CH ₃ CHO	-6199.390600	+60.26
2	5.2 (<i>i</i> PrOH).PhCOCN-tsE + PhCOCN + 8.2 (<i>i</i> PrOH) + CH ₃ CHO	Not calculated	Not calculated
3	5.2 (<i>i</i> PrOH).PhCOCN-tsA + PhCOCN + 8.2 (<i>i</i> PrOH) + CH ₃ CHO	-6199.4135397	+45.87
4	6.2 <i>i</i> PrOH + 2(<i>i</i> PrOH) + 2PhCOCN + CH ₃ CHO	-6199.439976	+29.28
5	6 + 2(<i>i</i> PrOH) + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.4452498	+25.97
6	8 + 2(<i>i</i> PrOH) + biphelam + 2PhCOCN + CH ₃ CHO	-6199.464084	+14.15
7	7 + 2(<i>i</i> PrOH) + biphelam + 2PhCOCN + CH ₃ CHO	-6199.467058	+12.28
8	7.2 (<i>i</i> PrOH) + biphelam + 2PhCOCN + CH ₃ CHO	-6199.4788594	+4.88
9	8.2 (<i>i</i> PrOH) + biphelam + 2PhCOCN + CH ₃ CHO	-6199.484775	+1.16
10	2biphelam + 2Ti(OiPr) ₄ + 2PhCOCN + CH ₃ CHO	-6199.486630	0
11	9 + 2(<i>i</i> PrOH) + biphelam	-6199.486705	-0.05
12	7 _{TINC} -ts _{Re} + biphelam + 2PhCOO <i>i</i> Pr + 2HCN	-6199.487437	-0.51
13	7 _{TINC} -ts _{Si} + biphelam + 2PhCOO <i>i</i> Pr + 2HCN	-6199.490587	-2.48
14	5 _{LABB} -ts _{Re} + biphelam + Ti(OiPr) ₄ + HCN + 2PhCOO <i>i</i> Pr	Not found	Not found
15	5 _{LABB} -ts _{Si} + biphelam + Ti(OiPr) ₄ + HCN + 2PhCOO <i>i</i> Pr	-6199.501211	-9.15
16	8 _{LABB} -ts _{Re} + biphelam + 2PhCOO <i>i</i> Pr + HCN	-6199.505884	-12.08
17	9.2 (<i>i</i> PrOH) + biphelam + 2PhCOCN + CH ₃ CHO	-6199.507042	-12.81
18	2 x 10 + 2PhCOCN + CH ₃ CHO	-6199.507280	-12.96
19	8 _{LABB} -ts _{Si} + biphelam + 2PhCOO <i>i</i> Pr + HCN	-6199.509554	-14.39
20	9 _{TINC} -ts _{Si} + biphelam + HCN + 2PhCOO <i>i</i> Pr	-6199.512783	-16.41
21	9 _{TINC} -ts _{Re} + biphelam + HCN + 2PhCOO <i>i</i> Pr	-6199.513107	-16.61
22	2 x 5.2 (<i>i</i> PrOH) + 2PhCOCN + CH ₃ CHO	-6199.516105	-18.50
23	5 .HNC + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr + CH ₃ CHO	-6199.516572	-18.79
24	8 + biphelam + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.518733	-20.14
25	5 _{TINC} -ts _{Si} + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-6199.519952	-20.91
26	7 + biphelam + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.521708	-22.01
27	5 _{TINC} -ts _{Re} + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-6199.523364	-23.05
28	5 .HNC.CH ₃ CHO + 5.2 (<i>i</i> PrOH) ₄ + HCN + 2PhCOO <i>i</i> Pr	-6199.5024224	-23.59
29	8 .HCN.CH ₃ CHO + biphelam + 2PhCOO <i>i</i> Pr + 2HCN	-6199.525166	-24.18
30	5 NC ⁺ H ⁺ + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr + CH ₃ CHO	-6199.528900	-26.52
31	5 + 5.2 (<i>i</i> PrOH) + 2PhCOO <i>i</i> Pr + 2 HCN + CH ₃ CHO	-6199.529287	-26.76
32	5 NC ⁺ H ⁺ .CH ₃ CHO _{re} + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-6199.531684	-28.27
33	5 CN ⁺ H ⁺ + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr + CH ₃ CHO	-6199.531684	-28.27
34	5 NC ⁺ H ⁺ .CH ₃ CHO _{re} + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-6199.533720	-29.55
35	9 NC ⁺ H ⁺ + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.535357	-30.58
36	5 .HCN + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr + CH ₃ CHO	-6199.535559	-30.70
37	9 CN ⁺ H ⁺ + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.536443	-31.26
38	5 NC ⁺ H ⁺ .CH ₃ CHO _{si} + 5.2 (<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	-6199.538287	-32.42

39	5.HCN.CH ₃ CHO + 5.2(<i>i</i> PrOH) + HCN + 2PhCOO <i>i</i> Pr	6199.541203	-34.25
40	9 + biphelam + 2PhCOO <i>i</i> Pr + 2HCN + CH ₃ CHO	-6199.541354	-34.34
41	5 + 5.2(<i>i</i> PrOH) + CH ₃ CH(OH)CN + HCN + 2PhCOO <i>i</i> Pr	-6199.55532	-34.85

Moreover, as expected for a non-Curtin-Hammett-like scheme, the system was found to be highly sensitive to the ligand:Ti(O*i*Pr)₄ ratio. Thus, whereas 5.2(*i*PrOH) is the major complex in a 1:1 Binolam:Ti(O*i*Pr)₄ mixture, the relative amount of complexes varies significantly for 1:*n* Binolam:Ti(O*i*Pr)₄ mixtures. Actually, as shown in Scheme 9 and Table 2, dinuclear complex 9.2(*i*PrOH) is the most stable species for 1:2 and 1:3 Binolam:Ti(O*i*Pr)₄ mixtures. Accordingly, in a non-Curtin-Hammett framework the most abundant catalyst in these instances should likely be 9. Since calculations actually reveal that transition structures 9_{NC-ts_{Re}} and 9_{NC-ts_{Si}} are almost identical in energy (see Table 6 above) we can predict the formation of (almost) racemic *O*-benzoyl cyanohydrins 4. This expectation nicely fits the experimental observations, thus providing strong support to the non-Curtin-Hammett nature of benzoylcyanations catalyzed by Binolam:Ti(O*i*Pr)₄ mixtures. The available computational data does not allow us, however, to provide a satisfactory explanation for the observed inversion of enantioselection when using a 1:5 Binolam:Ti(O*i*Pr)₄ mixture. We speculate with the idea that the small energy difference between 9_{NC-ts_{Re}} and 9_{NC-ts_{Si}} might be inverted in solution, but the participation of species of higher nuclearity cannot be discarded.

Scheme 9. Computationally-determined (B3LYP/6-31G*) energy profiles of the benzoylcyanation of aldehydes catalyzed by 1:1 and 1:2 mixtures (shown in italics) of biphelam:Ti(O*i*Pr)₄.

3. Conclusions

DFT theoretical studies launched to get an insightful view of the mechanism of the enantioselective benzoylcyanation of aldehydes catalyzed by Binolam:Ti(O*i*Pr)₄ mixtures has led us to conclude that our reaction conditions are in fact non-Curtin-Hammett-like (Scheme 3), the main reason for this being that benzoylation of ligated *i*PrOH is a very slow reaction which takes place prior to the relevant cyanation. Experimental results fit well into this kinetic scheme, in particular 1) the preferential

formation of (*S*)-*O*-benzoyl cyanohydrins 4 when working with 1:1 (*R*)-Binolam:Ti(O*i*Pr)₄ as precatalytic mixture, 2) the formation of almost racemic *O*-benzoyl cyanohydrins 4 when working with 1:2 or 1:3 (*R*)-Binolam:Ti(O*i*Pr)₄ mixtures, and 3) the absence of NLE. A direct consequence of being in a non-Curtin-Hammett-like kinetic framework, is that optimization cannot be planned customarily, i.e. by means of the standard and systematic adjustment of operational variables, because for a non-Curtin-Hammett system products are the result of a kinetic quench of the competing routes that are available to all catalysts present in at a given time. In this regard, we believe that a successful approach for our cyanobenzoylations should involve the adjustment of structural variables in attempting to control the number and type of the actual precatalysts at work. In particular, our study shows that the presence of 9 in 1:1 mixtures should be avoided. An a priori plausible approach to get rid of 9 from 1:1 mixtures is to redesign the ligand so as to avoid its formation. Since the structure of 9 is characterized by having a wide dihedral angle along the axis of chirality, one line of action could be the use of a rigid ligand with a small dihedral angle so as to impede its formation. We plan to work in this direction.

4. Experimental Section

4.1. Computational details:

For the computational work we used a closed-shell DFT (B3LYP) treatment, as implemented in the Gaussian 03 package, with the 6-31G* basis set for all atoms.⁴⁸ As a prior check of the reliability of this method in dealing with titanium(IV) complexes, we optimized the dinuclear heterodimer whose x-ray diffraction structure has been described by Walsh et al.³⁸ The computational data resulting from DFT calculations using the B3LYP functional and one of two basis sets (BS-1: 6-31G* for all atoms, including titanium; BS-2: lan12dz for titanium and 6-31G* for all other atoms) nicely matched the X-ray data reported.⁴⁹ Eventually, we decided to use the BS-1 basis set (as for non-transition metal atoms all electrons are being considered for titanium).

The original input structures for DFT calculations were the optimized structures resulting from prior semiempirical work (not shown) carried out with PM3, the input data for PM3 calculations being itself derived from molecular mechanics conformational searches carried out with the MMFF force field, as implemented in the Spartan'04 package.⁵⁰ It is worth mentioning that Spartan uses "sampling" of the conformational space as opposed to complete scrutiny (being so flexible molecules, it should be recognized that complete scrutiny is simply an impossible work in term of computing time), for which purpose Monte Carlo methods are employed by default in the above application. Eventually, electron correlation was incorporated, in part, to our studies by means of density functional theory (DFT) calculations,^{51,52} by using the non-local hybrid three-parameter functional developed by Becke and denoted B3LYP exchange-correlation functional.⁵³ It must be emphasized that optimizations have been carried out using keywords for tight convergence criteria as well as for 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),

except for the case of solvated dimer **6.2iPrOH** due to its enormous size and minor relevancy.⁵⁴ 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. The cartesian coordinates of all the optimized structures described in this article are available from the main author.

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$$D/[C] = k_D[B]/k_C[A]$$
The stationary state approach as applied to A and B establishes that:

$$d[A]/dt = 0 = k_A[a] - k_C[A] \text{ and thus } [A] = k_A[a]/k_C$$

$$d[B]/dt = 0 = k_B[b] - k_D[B] \text{ and thus } [B] = k_B[b]/k_D$$
Equating the above equations and considering that $K = [b]/[a]$ one obtains:

$$[D]/[C] = k_D k_B [b] k_C / k_C k_A [a] k_D = k_B [b] / k_A [a] = K k_B / k_A$$
Therefore, for the case where $k_B \approx k_A$, then :

$$[D]/[C] = K$$
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