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Asymmetric synthesis of *O*-benzoyl cyanohydrins by reaction of aldehydes with benzoyl cyanide catalysed by BINOLAM–Ti(IV) complexes

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Abstract—The asymmetric cyanobenzoylation of aldehydes has been carried out for the first time, by reaction with benzoyl cyanide in a process catalysed by either (*R*)- or (*S*)-3,3′-bis(diethylaminomethyl)-1,1′-binaphthol BINOLAM–Ti(IV) complexes at room temperature and without additives. The reaction can be described as an overall cyano-*O*-benzoylation of aldehydes where a Lewis acid–Brönsted base (LABB) dual role for the catalyst induced firstly the key enantioselective hydrocyanation, which is then followed by *O*-benzoylation furnishing enantioenriched *O*-benzoyl cyanohydrins.

1. Introduction

Homochiral cyanohydrins are of synthetic interest as they can be transformed into a number of relevant functional groups such as β-amino alcohols, α-hydroxyacids, α-hydroxyesters, α-sulfonyloxynitriles, α-aminonitriles, α-fluoronitriles, 3-amino-2-alkenoates and substituted azacycloalkanes.[1] Many of them are key chiral building blocks in the synthesis of both biologically active natural products and therapeutically important molecules. The synthesis of nonracemic cyanohydrins and their *O*-protected derivatives can be accomplished by enzymes,[1b,c,2] organocatalysts[1] and metal complexes,[1] the latter being the most widely used over the last decade.[1c] A serious drawback of cyanohydrins and *O*-trimethylsilyl cyanohydrins is their instability due to the reversibility of the cyanohydrin formation. In addition, they are frequently prepared at very low temperatures while using highly toxic hydrogen cyanide or trimethylsilyl cyanide.[1] So, it is advantageous, from the synthetic point of view, to obtain chemically *O*-protected nonracemic cyanohydrins under very mild reaction conditions. In this sense, the *O*-alkoxycarbonyl cyanohydrins have been obtained from ketones and cyanoformates using *Cinchona* alkaloid-derived tertiary amines,[3] whilst the aldehydes reacted with ethyl cyanoformate and chiral bimetallic BINOL-derived yttrium(III) (YLB)[4] or titanium(IV)–salen complexes[5] and with methyl cyanoformate in the presence of a chiral 3,3′-bis(diethylaminomethyl)-1,1′-binaphthol (BINOLAM)-derived aluminium complexes.[6] These last complexes[7] and the above mentioned chiral bimetallic YLB-complex[8] were also involved in the enantioselective synthesis of the cyanohydrin *O*-phosphates, from aldehydes and diethylcyanophosphonate at room temperature and at −78 °C, respectively.

Recently, nonracemic *O*-acetyl cyanohydrins have been prepared with high enantioselection by employing chiral salen complexes of titanium(IV) **1**[9] and vanadium(V) **2**,[9] together with acetic anhydride and potassium cyanide as the cyanide source. The reaction of aldehydes, performed at −42 °C with the dinuclear titanium(IV) complex **1**, gave the *O*-acetyl cyanohydrins in good chemical yields and high enantiomeric excesses, whereas mononuclear vanadium(V)–salen complex **2** gave the same products with slightly lower ees.[9,10] A recyclable –titanium complex, based on structure **1**, was also evaluated in the same reaction obtaining *O*-acetyl cyanohydrins in very good yield and good enantioselection (up to 95.5:4.5 er) at −20 °C.[11,12] However, the asymmetric direct cyanobenzoylation of carbonyl compounds with acyl cyanides have not been described yet.

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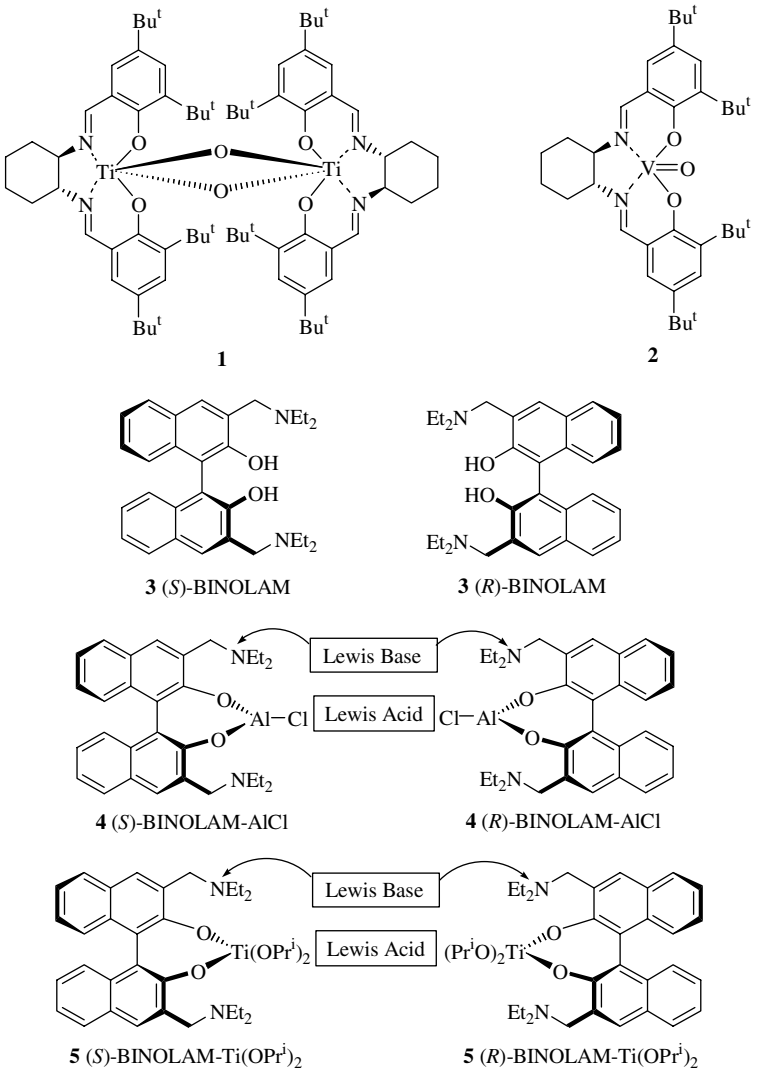
Continuing with the general study of chiral BINOLAM ligands **3**,[13] as part of the different bifunctional[14] metal complexes, and paying attention to the capability of BINOLAM–AlCl complex **4** to perform enantioselective addition of species containing a cyanide source onto aldehydes, such as TMSCN,[15] MeO_2CCN[6] and $(EtO)_2$-POCN,[7] we herein, report the cyanobenzoylation of aldehydes catalysed by the BINOLAM–Ti(IV) complexes.

of (*S*)-BINOLAM and dimethylaluminium chloride, did not give any reaction product, using toluene as solvent, when benzaldehyde or 3-phenylpropanal were employed as substrates. However, the complex derived from (*S*)-BINOLAM and titanium tetraisopropoxide furnished, at room temperature and in THF, quantitative yields and good enantioselection of products **6** (Scheme 1 and Table 1). Cyanohydrin derivative **6a** (R = Ph) was obtained in an 84:16 enantiomeric ratio

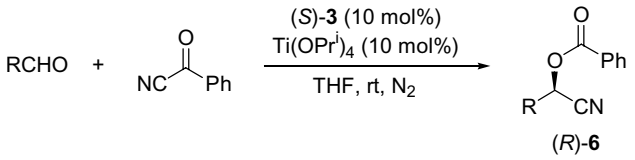


2. Results and discussion

The optimisation of the reaction conditions of the enantioselective synthesis of *O*-acyl cyanohydrins was done simultaneously for benzaldehyde and 3-phenylpropanal. Benzoyl cyanide was selected as the cyanide source because acetyl cyanide did not promote the reaction, giving very low chemical yields of the corresponding *O*-acetyl cyanohydrins. Following the previous enantioselective cyanation reaction conditions described for BINOLAM–AlCl complexes **4**,[6,7,15] we first studied the effect of the aluminium species in this reaction. Thus, complex (*S*)-**4**, obtained by mixing equimolar amounts

whilst **6h** was isolated in an 83:17 enantiomeric ratio (Scheme 1 and Table 1, entries 1 and 10, respectively).

The presumed monometallic (*S*)-BINOLAM–titanium(IV) **5** (10 mol %) was used as a catalyst for the enantioselective preparation of *O*-benzoyl cyanohydrins **6** from different series of aldehydes using THF as solvent at room temperature, under a nitrogen atmosphere (Scheme 1 and Table 1). The aromatic aldehydes (Table 1, entries 1–5) gave good chemical yields of the titled products **6** with good enantiomeric ratios (up to 84:16). Heteroaromatic aldehydes (Table 1, entries 6 and 7) behaved as in previous cyanation reactions pro-



Scheme 1.

moted by BINOLAM–AlCl complexes.[6,7,15] Only nicotinaldehyde offered a lower enantioselection, possibly because the heteroatom activates the benzoyl cyanide and consequently the racemic catalytic cycle. α,β-Unsaturated (Table 1, entry 8) and aliphatic aldehydes (Table 1, entries 9 and 10) also gave good enantiomeric ratios and chemical yields. The (*R*)-cyanohydrin *O*-benzoates could be obtained by using the (*R*)-BINOLAM–Ti(O-Pr^i)$_2$ complex **5** furnishing (*S*)-**6** in similar yield and enantiomeric ratio (Table 1, entry 2). The (*S*)-**5** complex always gave *O*-benzoyl cyanohydrin **6** with an (*R*)-configuration except in the example of furfural where (*S*)-**6d** was obtained due to a change in the priority of the substituents around the stereogenic centre. As previously described, ligand **3** could be recovered in an almost quantitative yield (92%) under extractive work-up[6,7,15,16] and reused without any loss of activity in the same transformation, for instance, compound (*R*)-**6a** was prepared in good yield and in an 84/16 er in the same reaction time (Table 1, entry 3). The reaction was monitored by GC and when judged complete was quenched with a 2 M aqueous solution of hydrochloric acid.[16] The enantiomeric ratios of products **6** were determined by chiral HPLC or chiral GC analysis while the absolute configuration was established according to the comparison of their specific rotations with the corresponding ones obtained from enantiomerically pure samples.

Many derivatives of these types of cyanohydrins have been employed for multiple purposes in various scientific areas. For instance, compound **6a** can be considered as a precursor of various cyanogenic glycosides isolated from the leaves and roots of *Phyllagatis rotundifolia*;[17] **6b** is a useful starting material in the synthesis of the natural products (−)-tembamide and (−)-aegeline[7,18] and **6f** can be employed in the elaboration of sphingosines[19] and coriolic acid.[20]

The mechanism of this reaction involves either a direct cyanobenzoylation or a cyanation followed by benzoylation, the latter being the most consistent hypothesis as it has been proven in other cyanation reactions catalysed by complexes **4**.[15] We propose the formation of a possible catalytically active species **5**, which would coordinate strongly the aldehyde by the Lewis acid centre and weakly the aldehydic hydrogen to an oxygen atom of a isoproxide moiety to afford species **7** (Scheme 2). The small amount of hydrogen cyanide, contained in the commercial benzoyl cyanide, is enough to give complex **8**, in which both reagents are simultaneously activated completing a real bifunctional catalysis activating both nucleophilic and electrophilic species. The role of the diethylaminomethyl arm as a Brönsted base seems to be crucial because, when using chiral BINOL as ligand, the reaction failed. Finally, and after the cyanide ion addition, the alcoholate in intermediate **9** would be benzoylated by an equivalent of benzoyl cyanide regenerating the catalytic amount of hydrogen cyanide and yielding the final *O*-benzoyl cyanohydrin **6**.

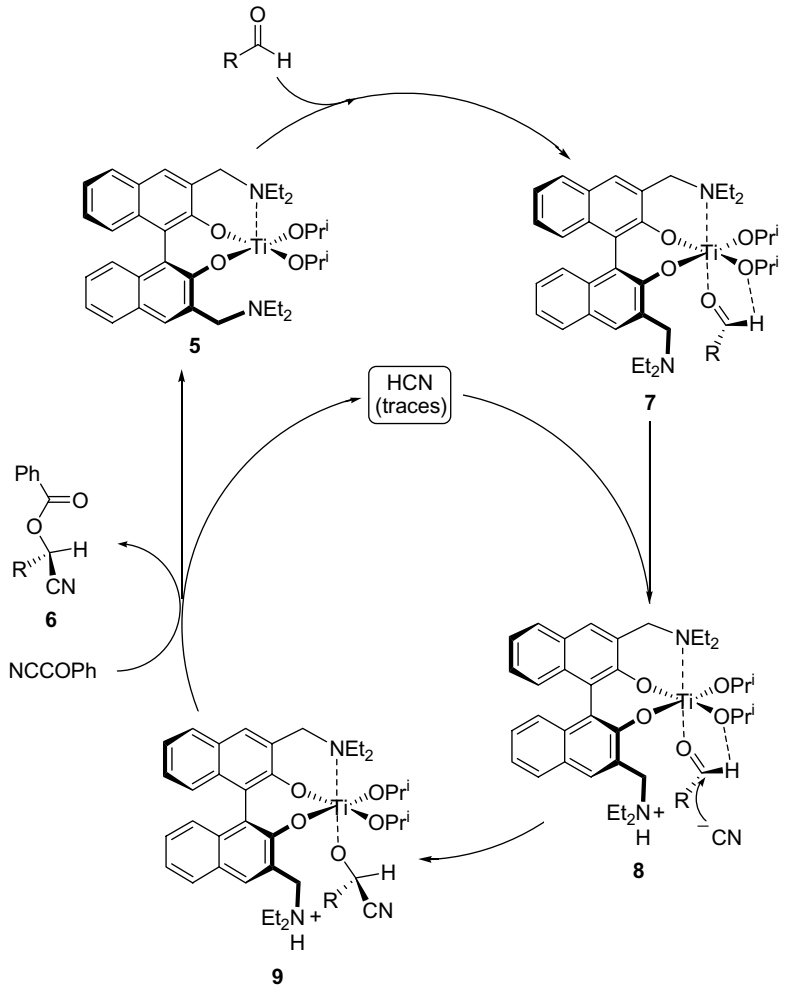
3. Conclusions

This work reports, for the first time, the enantioselective cyanobenzoylation of aldehydes using benzoyl cyanide and the BINOLAM–Ti(IV) complex as a catalyst, in good chemical yields, and easily recovering the chiral ligand BINOLAM **3**. In only one step, under mild reaction conditions (room temperature), enantiomerically enriched *O*-benzoylated cyanohydrins can be easily obtained. A bifunctional mechanism has been proposed based on a hydrogen cyanide addition followed by the

Table 1. Enantioselective synthesis of *O*-benzoyl cyanohydrins **6**

Entry	R	Time (h)	**6**	Yield[a] (%)	er[b]	ee
1	Ph	6	(*R*)-**6a**	91	84:16[c]	68
2	Ph[d]	6	(*S*)-**6a**	90	16:84[c]	68
3	Ph[e]	6	(*R*)-**6a**	90	84:16[c]	68
4	4-(MeO)C$_6$H$_4$	21	(*R*)-**6b**	76	79:21	58
5	4-ClC$_6$H$_4$	18	(*R*)-**6c**	85	79:21	58
6	2-Furyl	7	(*S*)-**6d**	89	78:22	56
7	3-Pyridyl	22	(*R*)-**6e**	93	64:26[f]	38
8	*E*-C$_5$H$_{11}$CH=CH	6	(*R*)-**6f**	87	84:16[g]	68
9	C$_6$H$_{13}$	12	(*R*)-**6g**	80	78:22[h]	56
10	PhCH$_2$CH$_2$	3	(*R*)-**6h**	93	83:17[f]	66

[a] Isolated yields after flash chromatography.
[b] Determined by chiral HPLC (Daicel, Chiralpak AS).
[c] Determined by chiral HPLC (Daicel, Chiralpak AD).
[d] (*R*)-BINOLAM (*R*)-**3** was used.
[e] Recovered ligand (*S*)-**3** was employed.
[f] Determined by chiral HPLC (Daicel, Chiralcel OD-H).
[g] Determined by chiral HPLC (Daicel, Chiralcel OJ).
[h] Determined by chiral GC (γ-cyclodextrin).



Scheme 2.

O-benzoylation. Ab initio and DFT calculations, as well as NMR experiments, are in progress and will be reported in due course with the aim of supporting these hypotheses.

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16. *Typical procedure*: To a solution of (*R*)- or (*S*)-BINOLAM[15] (0.025 mmol, 11.4 mg), in dry THF (1 mL), under dry atmosphere (argon), titanium tetraisopropoxide (0.025 mmol, 9 μL) was added, and the suspension stirred for 1 h at room temperature. Freshly distilled aldehyde (0.25 mmol) followed by the benzoyl cyanide (0.75 mmol, 90 μL) were added. The reaction was monitored by ^{1}H NMR or GC and when it was judged complete, HCl 2 M (2 mL) and ethyl acetate (2 mL) were added and the mixture stirred for 10 min. The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated under vacuo, and the crude purified by flash chromatography to obtain pure benzoyl-*O*-cyanohydrin **6** in yields shown in Table 1. The aqueous layer was treated with a 1 M NH_3/1 M NH_4Cl buffer solution and then extracted with ethyl acetate (2×10 mL); the organic layers were dried over $MgSO_4$ and evaporated, to yield (*S*)-BINOLAM in 96% (11 mg).
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