Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 10487–10496

Enantioselective addition of trimethylsilyl cyanide to aldehydes catalysed by bifunctional BINOLAM-AlCl versus monofunctional BINOL-AlCl complexes

Jesús Casas,[a] Carmen Nájera,[a,*] José M. Sansano[a] and José M. Saá[b,*]

[a]*Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apartado 99, 03080 Alicante, Spain*
[b]*Departament de Química, Universitat de les Illes Balears, 070122-Palma de Mallorca, Spain*

Received 23 April 2004; revised 7 June 2004; accepted 25 June 2004

Available online 24 August 2004

Abstract—A highly enantioselective cyanation of aldehydes takes place by using a bifunctional catalyst derived from 3,3′-bis(diethylaminomethyl) substituted binaphthol (BINOLAM) and dimethylaluminium chloride. The addition is of wide scope and runs best in toluene at temperatures ranging from −20 to −40 °C, in the presence of 4 Å MS and triphenylphosphine oxide as additives. The (*R*)- or (*S*)-cyanohydrins result when using (*S*)- or (*R*)-BINOLAM-AlCl complexes, respectively. The valuable ligand can be recovered by simple extractive work-up and recycled without loss of efficiency (both in terms of chemical and stereochemical yields). This methodology is applied to the Shibasaki synthesis of epothilone A. All the evidence available for the BINOLAM-AlCl enantioselective addition of TMSCN to aldehydes call for the intervention of a hydrocyanation reaction, addition of a catalytic amount of hydrogen cyanide, generated in situ, to an aldehyde, followed by *O*-silylation. In order to determine the role of the basic amino groups of BINOLAM, comparative studies are carried out with the monofunctional 1,1′-binaphthol-derived complex BINOL-AlCl.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The preparation of non-racemic cyanohydrins is an important goal for current asymmetric organic synthesis.[1] The reason for this is clear-cut: enantiomerically pure cyanohydrins are important building blocks for the synthesis of several 1,2-bifunctional products such as α-hydroxycarbonyl compounds, β-amino alcohols, α-amino acids and new materials.[1,2] Ten years ago, cyclic peptides and enzymes were overwhelmingly used in the synthesis of non-racemic cyanohydrins rather than chiral metal complexes,[2d] but this order has nowadays been completely reversed.[2a] Many metal complexes have been successfully employed as Lewis acids for the addition of HCN or TMSCN to aldehydes and ketones,[2] as for example, magnesium, zirconium, titanium, aluminium, yttrium, lanthanum, samarium, vanadium and gadolinium complexes containing mono- or polydentate ligands.[2] Nakai et al.[3] were the first to employ monofunctional BINOL-metal complexes (titanium in particular) for the enantioselective cyanosilylation of aldehydes, but only observed modest enantioselectivity for aliphatic aldehydes. Fortunately though, a new generation of bifunctional BINOL-derived complexes[2a,4] emerged as valuable synthetic tools. These catalysts possess functional groupings to simultaneously bind a basic substrate and an acidic reactant in a proper manner so that rate, among other factors, is favourably affected.[2a,4] In particular, Shibasaki et al. reported a series of bifunctional Lewis Acid-Lewis Base catalysts (LALB) **1** (Fig. 1) derived from BINOL as the chiral scaffold where an aluminium atom of a bisaryloxyaluminium chloride moiety functions as the Lewis acid centre (LA) and a suitable functionality at the 3,3′ positions works as the Lewis base centre (LB).[5] Specifically, the phosphine oxide-derived catalysts **1** (R=H, X=$POAr_2$) were found to be very efficient for the asymmetric cyanosilylation of aldehydes,[6] imines[7] (Strecker synthesis) and isoquinolines[8] (Reissert-type reaction). As an added-value goal, a polymer-supported catalyst **1** [R=linker-(polymer, X=$P(O)Ph_2$] was eventually developed in order to recover and recycle the chiral ligand, however with some loss of enantioselectivity.[7]

Recently, we have developed a bifunctional Lewis Acid-Brönsted Base (LABB) aluminium complex, namely (*S*)- or (*R*)-BINOLAM-AlCl **3**, which retains the C_2-symmetric BINOL scaffold but possesses two diethylaminomethyl arms, instead of the phosphine oxide ones, presumably working as Brönsted bases.[9–11] BINOLAM-AlCl complexes

Keywords: Asymmetric catalysis; Cyanohydrins; Binolam; Binol; Aluminium complex.
* Corresponding authors. Tel./fax: +34-965903549 (C.N.); tel.: +34-97117326 (J.M.S.); e-mail addresses: cnajera@ua.es; jmsaa@uib.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.137

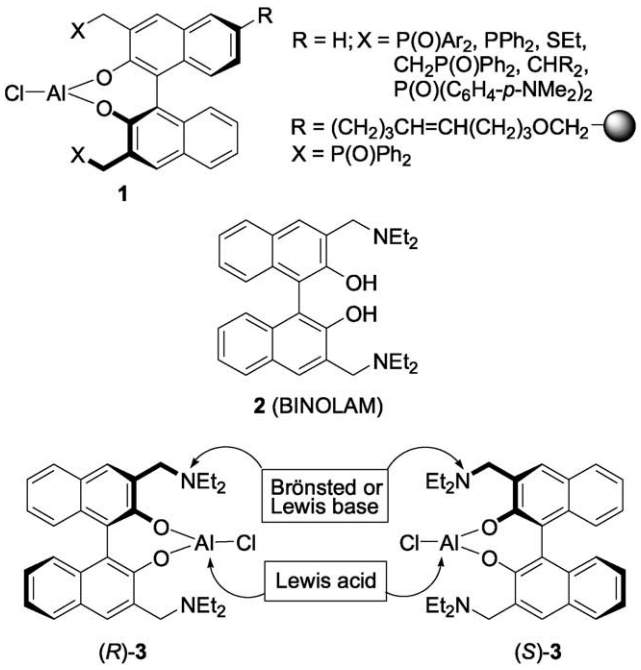
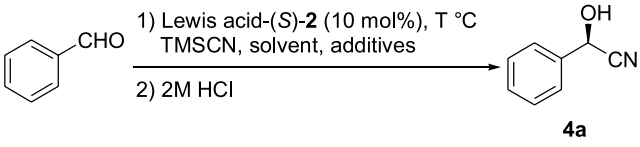


Figure 1.

have been proved to be versatile bifunctional catalysts in the asymmetric synthesis of cyanohydrins,[9] *O*-methoxycarbonyl cyanohydrins[10] and *O*-phosphorylated cyanohydrins[11] from aldehydes, in excellent chemical yields and very high enantiomeric ratios using TMSCN, $CNCO_2Me$ and $CNPO(OEt)_2$ as cyanation agents, respectively. In continuing with our studies on the synthetic applications of chiral (*S*)- and (*R*)-BINOLAM-AlCl complexes, we describe in this article a comprehensive study of these catalysts for the enantioselective synthesis of cyanohydrins upon reaction of aldehydes with TMSCN.[9] Also, as a reference point, this analysis includes the study of the enantioselective catalysis promoted by the analogous monofunctional BINOL-AlCl catalyst.

2. Results and discussion

The optimisation of the variables of the reaction between benzaldehyde and commercial TMSCN was started by examining a number of selected Lewis acids and additives (Scheme 1 and Table 1). For this purpose, all catalysts were generated in situ by mixing a weighed amount of the ligand **2**[12] (BINOLAM, 10 mol%, relative to aldehyde) with the appropriate Lewis acid (10 mol%), at room temperature for 1 h, in the selected solvent. This operation was then followed by the addition of benzaldehyde and commercial TMSCN (300 mol%) in one portion, at 0 °C, in the presence of 4 Å molecular sieves (MS) (200 mg/mmol of aldehyde). The reaction was monitored by ^{1}HNMR spectroscopy and, at the end, after acidic extractive workup with 2 M hydrochloric acid (more advantageous than neutral workup which led to mixtures of partially silylated cyanohydrins), we isolated the pure cyanohydrin **4a**. Its enantiomeric purity, and those of other cyanohydrins **4** was checked by HPLC (Chiracel OD-H, Chiralpack AD and AS) on appropriate derivatives (see Section 3 for details). The acidic aqueous phase was treated with a buffered solution of 1 M ammonia/1 M ammonium chloride until the pH turned basic. Upon extraction with ethyl acetate we recovered ligand **2** (BINOLAM) in almost quantitative yield (>95%) and purity (>98% according to its optical rotation).



Scheme 1.

Initial experiments with titanium(IV) complexes, generated with $TiCl_2(OPr^i)_2$ or $Ti(OPr^i)_2$, gave satisfactory enantiomeric ratios (er) when working in toluene in the presence of 4 Å molecular sieves, even slightly better than the aluminium(III) complex obtained from dimethylaluminium chloride (Table 1, entries 1–4). However, unlike the

Table 1. Cyanation of benzaldehyde catalysed by preformed Lewis acid (*S*)-**2** complexes

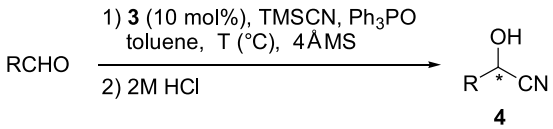
Run	Lewis acid	Solvent	Additives	*T* (°C)	*T* (h)	**4a** (%)[a]	er[b]
1	$TiCl_2(OPr^i)_2$	CH_2Cl_2	4 Å MS	0	24	65	55/45
2	$TiCl_2(OPr^i)_2$	$PhCH_3$	4 Å MS	0	24	83	88/12
3	$Ti(Opr^i)_4$	$PhCH_3$	4 Å MS	0	1	99	78/22
4	$AlClMe_2$	$PhCH_3$	4 Å MS	0	26	87	67/33
5	$AlClMe_2$	$PhCH_3$	4 Å MS/Ph_3PO	0	3	99	88/12
6	$AlClEt_2$	$PhCH_3$	4 Å MS/Ph_3PO	0	8	99	90/10
7	$AlClMe_2$	CH_2Cl_2	4 Å MS/Ph_3PO	0	14	99	77/23
8	$AlClMe_2$	$PhCH_3$	Ph_3PO	0	20	99	75/25
9	$AlClMe_2$	$PhCH_3$	4 Å MS/Ph_3PO	−20	6	99	>99/1
10	$AlClMe_2$[c]	$PhCH_3$	4 Å MS/Ph_3PO	−20	6	99	>1/99
11	$AlClMe_2$	$PhCH_3$	3 Å MS/Ph_3PO	−20	16	83	94/6
12	$AlClMe_2$	$PhCH_3$	5 Å MS/Ph_3PO	−20	9	99	91/9
13	$AlClMe_2$[d]	$PhCH_3$	4 Å MS/Ph_3PO	−20	12	89	96/4
14	$AlMe_3$	$PhCH_3$	4 Å MS/Ph_3PO	−20	4	99	50/50
15	$AlCNEt_2$	$PhCH_3$	4 Å MS/Ph_3PO	−20	3	99	55/45

[a] The isolated yields given refer to the cyanohydrins obtained after acidic hydrolysis.
[b] Enantiomeric ratios were determined by chiral HPLC analysis (Chiralcel OD-H).
[c] Reaction performed with (*R*)-BINOLAM.
[d] A 5 mol% charge of (*S*)-**3** was used as catalyst.

titanium complexes, the activity of the aluminium complex could be further modulated by manipulation of additives and temperature. For this reason, we then focussed our study on the enantioselective addition of TMSCN to aldehydes catalysed by aluminium(III) complexes. A crucial discovery to the optimisation process was the favourable effect observed on addition of triphenylphosphine oxide (40 mol%)[6] to the aluminium complexes,[13] which led to an increase of both reaction rate and er (Table 1, entries 4 and 5). In the course of these optimisations we also recognized the importance of a second additive, namely 4 Å MS.[14] Mediocre results (both in terms of rate and er) were obtained in its absence (Table 1, entry 8), whereas in the presence of 4 Å MS, dried at 120 °C for 4 h, excellent results were obtained (Table 1, entry 5). Thermogravimetric analysis of this partially dried 4 Å MS revealed the presence of 7.5% of water content. On the other hand, the use of ultradried 4 Å MS (200 °C, 6 h, under high vacuum) led to an extremely slow reaction. So, a small amount of water seemed to be required for activity.[15] However, water itself can not be used, as suggested by the fact that operating without 4 Å MS, but in the presence (added at the start in one portion) of an equivalent amount of water leads to cyanohydrin **4a** in very low yield and enantiomeric ratio, possibly because water destroys the catalyst. Accordingly we realised at this point that 4 Å MS were possibly acting as an excellent carrier of a limited amount of water, as recently demonstrated for a similar reaction.[16] So, what is the role of water? Since water could induce a limited hydrolysis of TMSCN to HCN, we examined and proved by NMR (^{1}H and ^{13}C) that adding either water or 4 Å MS to an NMR tube containing TMSCN produced HCN. It appeared then that, under these reaction conditions, the enantioselective addition of trimethylsilyl cyanide to the aldehyde was actually a hydrocyanation reaction followed by *O*-silylation. The use of 3 or 5 Å MS also led to excellent er, at −20 °C, but nevertheless inferior to those obtained with 4 Å MS (Table 1, entries 9, 11 and 12). In further optimising work we also learned that the highest er was reached by operating at −20 °C in the presence of triphenylphosphine oxide (40 mol%) and 4 Å MS in toluene as solvent (the mixture was somewhat heterogeneous in this solvent). Other suitable solvents such as dichloromethane (Table 1, entries 5 and 7), THF, chloroform and diethyl ether (not included in Table 1) led to poorer results. As precursory aluminium species we found dimethylaluminium chloride to be preferred over diethylaluminium chloride because the former induced a faster reaction (Table 1, entries 5 and 6). On the other hand, trimethylaluminium or, more interestingly, diethylaluminium cyanide led to no asymmetric induction (Table 1, entries 14 and 15), thereby proving that aluminium cyanide species were not the key derivatives involved in the enantioselective cyanation observed. The best catalyst charge was established as 10% molar (relative to aldehyde), after realising that a substantial reduction in rate occurred using a 5% molar charge (Table 1, entry 13).

Concerning the stereochemical issues, we noticed the following systematic trends: the (*S*)-BINOLAM-AlCl complex leads to the enantiomerically enriched (*R*)-configured cyanohydrins **4**, and the opposite was also true: (*R*)-BINOLAM-AlCl complex leads to (*S*)-configured cyanohydrins **4** (Table 1, entries 2, 6, 10). The only exception to this rule, namely that of furfural, is simply due to a change in the CIP priority of the substituents. Absolute configurations were assigned on the basis of literature data (see Section 3 for individual details). The enantiomeric ratios reported here were determined by chiral HPLC (Chiralcel OD-H and Chiralpack AD and AS) analyses of the corresponding *O*-acetyl, *O*-benzoyl, *O*-TMS, or *O*-TBDMS cyanohydrins (see Section 3 for individual details). Prior control tests demonstrated that no racemisation occurred during these derivatisations. So, it can be taken for granted that the enantiomeric ratios given actually represent the enantiomeric ratios of cyanohydrins themselves.

As shown below, the cyanation reactions appear to be of general applicability (Scheme 2 and Table 2). Thus, aromatic aldehydes led to the corresponding cyanohydrins with excellent er's and chemical yield by working at −20 °C (Table 2, entries 1–11). Somewhat lower er's were obtained for the case of *m*-phenoxybenzaldehyde, possibly because of the steric demand of the phenoxy group, as illustrated in Table 2 (entries 8 and 9). The behaviour of heteroaromatic aldehydes also provided indirect evidence in favour of the hydrocyanation mechanism. Thus, whilst furfural gave good results when lowering the temperature down to −40 °C (96/4 er), nicotinaldehyde behaved as a special case as it required a large excess of TMSCN for the reaction to give 99% yield (Table 2, entries 12–14), the enantioselectivity being always a mediocre 75/25 er. In this case, the heterocyclic nitrogen atom of the pyridine ring works as a basic site (Brönsted base, BB) to capture the HCN involved in the hydrocyanation reaction, thereby slowing down the reaction rate and facilitating the competition of non-asymmetric routes. Conjugated aldehydes were also suitable substrates for this cyanation reaction, the best er's being obtained when operating at −20 and −40 °C, depending on the structure of the aldehyde (Table 2, entries 15–17). Aliphatic aldehydes, on the other hand, gave cyanohydrins **4** in very good yields and er's when operating at −40 °C in short reaction times (Table 2, entries 18–22). For the particular case of heptanal, we checked the influence of (a) using an alkylphosphine oxide such as tri-*n*-butylphosphine oxide (40 mol%) instead of triphenylphosphine oxide, and (b) lowering the temperature to −60 °C, but no improvement was detected (Table 2, entries 20 and 21, respectively). The ketones did not react under these conditions, similarly as reported for the Shibasaki's conditions employing complexes **1**.[6]



Scheme 2.

Several operational advantages of our methodology with the BINOLAM-AlCl catalyst need to be mentioned: (a) the procedure is operationally simple as all reagents are added at once (no slow pump addition was needed as required by Shibasaki's method)[8] and takes place in short reaction times and easy-to-reach operating temperatures; (b) the chiral ligand employed is stable and it can be recovered almost

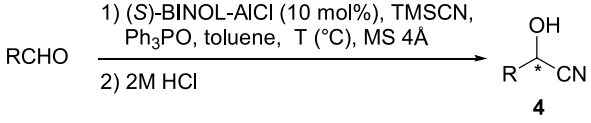
Table 2. Synthesis of enantiomerically enriched **4** catalysed by either (*R*)- or (*S*)-**3** complexes

Run	R	**3**	*T* (°C)	Time (h)	**4**	Yield (%)[a]	Conf.[b]	er[c]
1	Ph	(*S*)	−20	6	**4a**	99	(*R*)	>99/1
2	Ph	(*R*)	−20	6	**4a**	99	(*S*)	>99/1
3	Ph	(*S*)[d]	−20	6	**4a**	99	(*R*)	>99/1
4	4-(MeO)C_6H_4	(*S*)	−20	20	**4b**	99	(*R*)	>99/1
5	4-(Me_2N)C_6H_4	(*S*)	−20	22	**4c**	>95	(*R*)	99/1[e]
6	2-ClC_6H_4	(*R*)	−20	8	**4d**	99	(*S*)	98/2
7	4-ClC_6H_4	(*S*)	−20	21	**4e**	99	(*R*)	>99/1
8	3-(PhO)C_6H_4	(*S*)	−20	48	**4f**	70	(*R*)	85/15
9	3-(PhO)C_6H_4	(*S*)	−40	48	**4f**	45	(*R*)	89/11
10	3,4-(OCH_2O)C_6H_3	(*R*)	−20	24	**4g**	55	(*S*)	97/3
11	6-(MeO)-2-naphthyl	(*S*)[f]	−20	39	**4h**	90	(*R*)	95/5
12	3-Pyridyl	(*R*)	−20	8	**4i**	99	(*S*)	75/25[e]
13	2-Furyl	(*S*)	−20	5	**4j**	99	(*S*)	88/12
14	2-Furyl	(*S*)	−40	12	**4j**	99	(*S*)	96/4
15	(*E*)-C_5H_{11}CH=CH	(*S*)	−20	21	**4k**[g]	59	(*R*)	98/2
16	(*E*)-PhCH=CH	(*S*)	−20	6	**4l**	99	(*R*)	91/9
17	(*E*)-PhCH=CH	(*R*)	−40	12	**4l**	99	(*S*)	>99/1
18	$PhCH_2CH_2$	(*R*)	−40	4.5	**4m**	99	(*S*)	94/6[h]
19	$CH_3(CH_2)_5$	(*R*)	−40	3.5	**4n**	99	(*S*)	83/17[i]
20	$CH_3(CH_2)_5$[j]	(*R*)	−40	3.5	**4n**	99	(*S*)	65/35[i]
21	$CH_3(CH_2)_5$	(*R*)	−60	10	**4n**	87	(*S*)	65/35[i]
22	*c*-(C_6H_{11})	(*R*)	−40	12	**4o**	99	(*S*)	60/40[k]

[a] Isolated yields of the cyanohydrins **4** after acidic hydrolysis with 2 M hydrochloric acid, except for **4i**, which was obtained after quenching with water.
[b] Assigned by comparison to literature data.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H, Chiralpak AD and AS) on the corresponding *O*-acetyl derivatives.
[d] Reaction performed with recovered ligand obtained by extractive work-up and recrystallisation.
[e] Six equivalents of TMSCN were required.
[f] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TMS derivative.
[g] This compound was characterised as its methoxycarbonyl derivative.
[h] Determined by chiral HPLC analysis (Chiralcel OD-H) on the corresponding *O*-TBDMS derivative.
[i] Determined by chiral HPLC analysis (Chiralcel OD-H) on the corresponding *O*-benzoyl derivative.
[j] Tri-*n*-butylphosphine oxide (40 mol%) was added instead of triphenylphosphine oxide.
[k] Determined by chiral GC analysis (γ-cyclodextrin) of the corresponding *O*-methoxycarbonyl derivative.

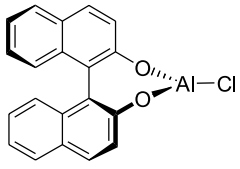
quantitatively and reused without loss in efficiency (Table 2, entry 3); (c) the process can be scaled-up to 2.5 mmol, at least, thereby affording compound **4a** after 12 h in >95% yield and 98.5/1.5 er.

We have made efforts to clarify the non-trivial classification of the BINOLAM-AlCl catalyst as being bifunctional or monofunctional. For that purpose, we focussed our attention on monofunctional complexes (*R*)- or (*S*)-BINOL-AlCl **5**, which lack the amino arms at C3 and C3′ characteristic of BINOLAM-AlCl, and comparatively studied their efficiency in the enantioselective addition of TMSCN to aldehydes. We prepared complex (*S*)-BINOL-AlCl **5** as described before for BINOLAM-AlCl, and then we optimised the conditions for the addition of TMSCN to benzaldehyde. Once again, we found that both triphenylphosphine oxide and 4 Å MS (7.5% water content) accelerated the reaction and pushed the enantioselectivity of the process towards excellence. Best results were actually obtained using (*S*)-BINOL-AlCl together with 4 Å MS (200 mg/mmol relative to aldehyde) and triphenylphosphine oxide (40 mol%), in toluene, at −20 °C. In this manner, after acidic workup (2 M HCl), cyanohydrin **4a** was isolated in high yield and er (Scheme 3, Table 3, entry 1). The total or partial absence of 4 Å MS and triphenylphosphine oxide did not benefit either the chemical or optical yields (Table 3, entries 1–3). As shown above for the catalysis by BINOLAM-AlCl, the key operation behind the overall addition of TMSCN to aldehydes catalysed by BINOL-AlCl **5**, under the above reaction conditions, should also be considered a hydrocyanation reaction.



4

Scheme 3.



5

The absence of a clear-cut basic site in BINOL-AlCl **5** (as compared to BINOLAM-AlCl **3**) suggested that addition of an external base might erode or even annihilate the enantioselectivity of the reaction by opening-up competing non-asymmetric processes. This reasoning was actually supported by experiment as the addition of a substoichiometric amount of triethylamine (20 mol%) to the otherwise standard reaction conditions led to almost racemic (er 60/40) product (Table 3, entry 6). This result also suggested that other basic centres in the substrates or otherwise, capable of capturing HCN might affect the chemical yield and/or result in lower enantioselectivities. The results actually found for a variety of aldehydes can be defined as capricious. Thus, arylaldehydes and heteroarylaldehydes and α,β-unsaturated aldehydes either did not react or afforded almost racemic cyanohydrins (Table 3,

Table 3. Synthesis of enantiomerically enriched **4** catalysed by the (*S*)-BINOL-AlCl complex

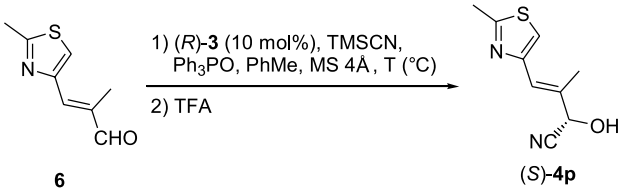
Run	R	*T* (°C)	Time (h)	**4**	Yield (%)[a]	Conf.[b]	er[c]
1	Ph[d]	−20	24	**4a**	9	(*R*)	—
2	Ph[e]	−20	24	**4a**	10	(*R*)	90/10
3	Ph[f]	−20	24	**4a**	11	(*R*)	92/8
4	Ph	−20	4	**4a**	99	(*R*)	96/4
5	Ph[g]	−20	3	**4a**	99	(*R*)	95/5
6	Ph[h]	−20	9	**4a**	99	(*R*)	60/40
7	4-(MeO)C_6H_4	−20	48	**4b**	24	—	50/50
8	4-ClC_6H_4	−20	24	**4e**	—	—	—
9	6-(MeO)-2-Naphthyl	−20	48	**4h**	40	(*R*)	56/44
10	3-Pyridyl[i]	−20	40	**4i**	99	(*R*)	97/3[j]
11	2-Furyl	−20	24	**4j**	—	—	—
12	(*E*)-C_5H_{11}CH=CH	−20	24	**4k**	—	—	—
13	(*E*)-PhCH=CH	−20	24	**4l**	—	—	—
14	$PhCH_2CH_2$	−20	12	**4m**	>95	(*R*)	90/10[k]
15	$PhCH_2CH_2$	−40	18	**4m**	>95	(*R*)	94/6[k]
16	$CH_3(CH_2)_5$	−20	14	**4n**	>95	(*R*)	54/46[l]

[a] Isolated yields of the cyanohydrins **4** after acidic hydrolysis using 3 equiv. of TMSCN.
[b] By comparison to known optical rotations.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H, Chiralpak AD and AS) of the corresponding *O*-acetyl derivatives.
[d] In the absence of both additives.
[e] In the absence of 4 Å MS.
[f] In the absence of triphenylphosphine oxide.
[g] The aluminium source was Et_2AlCN.
[h] 20 mol% of dry triethylamine was added.
[i] The reaction was quenched with water.
[j] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TMS derivative.
[k] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TBDMS derivative.
[l] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-benzoyl derivative.

entries 7–9 and 11–13). The case of nicotinaldehyde, however, came as a surprise as the cyanohydrin was obtained in high yield and er (Table 3, entry 10). This result is now understood as a consequence of the intermediate formation of the pyridinium salt, likely the actual species undergoing reaction. Aliphatic aldehydes, on the other hand, gave different results according to their structures (Table 3, entries 14–16), that suggest the likely influential role of CH-π interactions. Thus, whereas strictly aliphatic aldehydes yielded almost racemic mixtures (Table 3, entry 16), those having a β-phenyl substituent yielded the corresponding cyanohydrin in good chemical yield and er (Table 3, entries 14–15). As for the processes catalysed by (*S*)-BINOLAM-AlCl **3**, those catalysed by the (*S*)-BINOL-AlCl **5** complex gave (*R*)-configured cyanohydrins.

Some of the examples depicted in Tables 2 and 3 are interesting molecules, for example, **4a** is a part of new cyanogenic glycosides isolated from the leaves and roots of *Phyllagatis rotundifolia*,[17] **4b** is used in the synthesis of the naturally occurring (−)-tembamide and (−)-aegeline,[3,18] cyanohydrin **4f**[19,20] is an intermediate in the industrial production of pyrethroid insecticides,[21] compound **4d** is an intermediate in the synthesis of the anti-thrombotic agent clopidogrel,[22] cyanohydrins **4g** and **4i** are direct precursors of biogenic amines and chiral 2-amino-1-(3-pyridinyl)ethanol,[23] respectively, and product **4k** is employed in the preparation of sphingosines[24] and coriolic acid.[25] In addition, a direct application of this methodology was the elaboration of the key intermediate (*S*)-**4p**, used in the synthesis of epothilone A,[26] involving the cyanation of the aldehyde **6** containing a thiazole moiety (Scheme 4). Previously, compound (*S*)-**4p** was prepared at −40 °C in 48 h by adding 1.5 equiv. of TMSCN very slowly (syringe pump).[6b,27] In our case, slow addition of 2 equiv. of TMSCN was not productive (Table 4, entry 3) because a large amount of unreacted aldehyde **6** was observed in the crude reaction product. Fortunately, when the reaction was carried out at −20 °C using an excess of TMSCN (9 equiv.), added in one portion, the reaction was completed in 36 h in excellent chemical yield and very good enantiomeric ratio (Table 4, entry 4). Lowering the operating temperature to −40 °C did not produce a substantial improvement in the enantiomeric ratio of compound **4p** (Table 4, entry 5). It is worth noting that the thiazole ring (pK_a=2.4), is less basic than the pyridine ring (pK_a=5.2), and so is not able to induce by itself a racemic side-process. (*S*)-BINOL-AlCl **5** was also tested as a catalyst in this transformation but the yield was quite low and the cyanohydrin **4p** was finally isolated as a racemic mixture. In all of the examples the reaction was quenched by the addition of trifluoroacetic acid at −20 or −40 °C (see Table 4), the enantiomeric ratios were determined by chiral HPLC analyses (Daicel Chiralpak AD) of its *O*-TBDMS derivative and the absolute configuration was determined by comparing the optical rotation with that obtained from a pure sample.[6b]

The proposed mechanism for this reaction significantly departs from that reported by Shibasaki et al. in a number of



6 (*S*)-**4p**

Scheme 4.

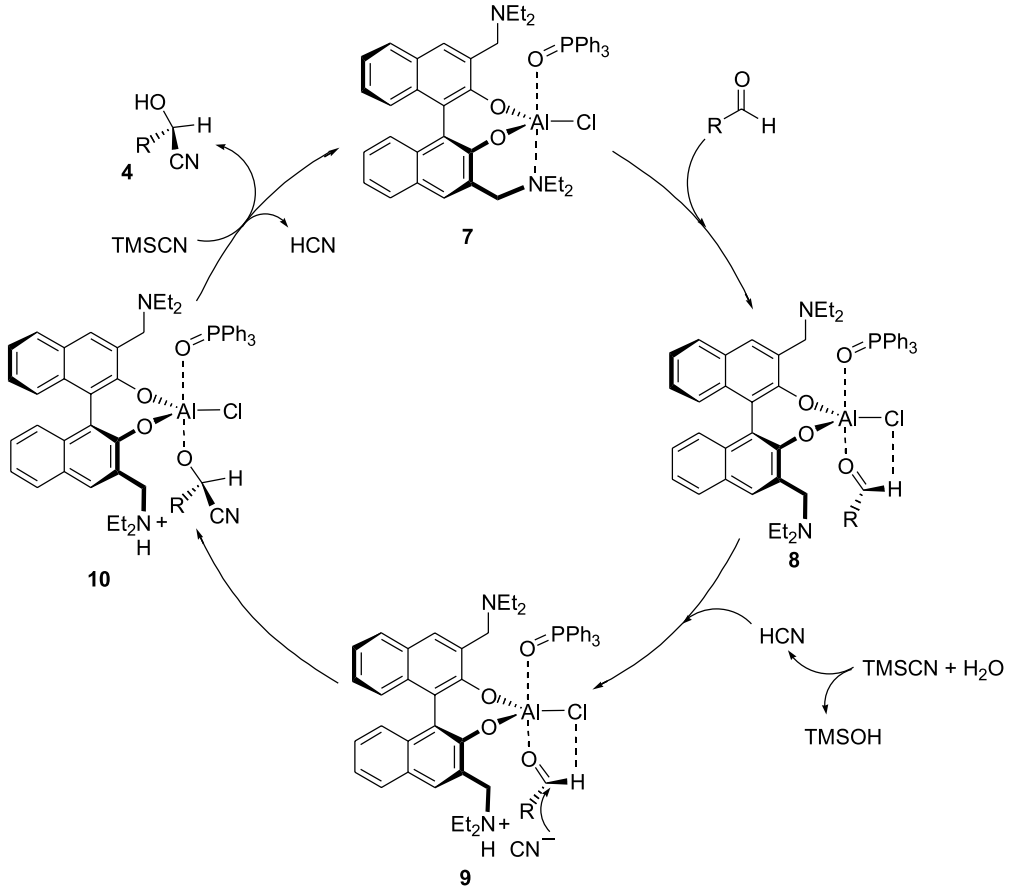
Table 4. Enantioselective synthesis of compound **4p**

Run	TMSCN (equiv)	*T* (°C)	T (h)	**4p** (%)[a]	er[b]
1	3	−20	22	33	96/4
2	1.5+1.5[c]	−20	48	52	88/12
3	2[d]	−20	24	0	—
4	9	−20	36	>98	96/4
5	9	−40	48	>98	96/4
6[e]	6	−20	24	54	50/50

[a] Isolated yields given refer to the cyanohydrin obtained after quenching the reaction with trifluoroacetic acid.
[b] Enantiomeric ratios were determined by chiral HPLC analysis (Chiralpak AD) of the *O*-TBDMS derivative.
[c] The second 1.5 equiv. of TMSCN was added after 1 d.
[d] Slow syringe pump addition over 24 h.
[e] Performed with (*R*)-BINOL-AlCl **5** complex.

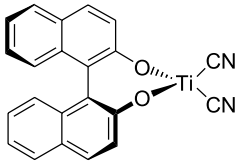
relevant issues. According to kinetic studies they showed that the two existing phosphine oxide units should play two different roles: the phosphine oxide located in the integrated arm of the ligand activated the trimethylsilyl cyanide while the added phosphine oxide was required to generate a pentavalent aluminium complex and prevent oligomerisation.[6,13] The study of the ^{31}P NMR spectra of an equivalent amount of BINOLAM-AlCl complex and triphenylphosphine oxide showed only one signal at 29.5 ppm (free triphenylphosphine oxide 30.1 ppm) supporting the existence of catalytic species **7** (Scheme 5). This reaction also presented linear effects when the enantiomeric excess of cyanohydrin **4a** was plotted versus the corresponding enantiomeric excess of the catalytic complex; unlike other reactions catalysed by chiral BINOLAM-AlCl **3** complexes, such as the asymmetric synthesis of *O*-methoxycarbonyl[10] and *O*-phosphorylated[11] cyanohydrins, which, in absence of triphenylphosphine oxide, exhibited moderate and strong positive non-linear effects (NLE),[28] respectively. The pentacoordinated, highly stable,[29] intermediate species **8** (Scheme 5) was proposed from the very broad band observed at 47 ppm in the ^{27}Al NMR experiment.[30]

The contribution of the chlorine to the catalytic cycle of BINOLAM-AlCl **3** complex was important; when it was not present the reaction was not so enantioselective as deduced from entries 14 and 15 of Table 1. A weak interaction of the aldehydic proton and the chlorine atom,[31] together with a stronger interaction between the carbonyl oxygen atom and the aluminium centre, presumably fixed the aldehyde to the chiral catalytic domain.

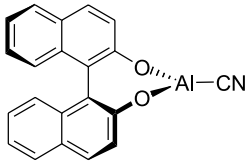


Scheme 5.

The ^{13}C and ^{1}H NMR spectra of equimolar mixtures of TMSCN/water of 4 Å MS, TMSCN/Ph_3PO and TMSCN/Et_3N revealed that water contained in 4 ÅMS interacted instantaneously to form hydrogen cyanide and trimethylsilanol and no noticeable chemical shifts, apart from the pure compound signals, were observed for the other two mixtures, thus indicating that triphenylphosphine and triethylamine are not so good activating agents of TMSCN. So, the small amount of HCN, generated by the water content of molecular sieves would react with a diethylamino group of the ligand in **9** (Scheme 5). As described above, if we add an exact amount of water (equivalent to the amount contained by the MS) the reaction failed and the er of **4a** was also very low working with extremely anhydrous molecular sieves (high vacuum, 200 °C, 6 h) or with molecular sieves saturated in water (overnight, air, rt). The diethylaminomethyl group would act as a Brönsted base capturing the HCN and, consequently, activating the nucleophile, which is supported by the fact that the addition of a competing base such as triethylamine (20 mol%), at −20 °C, lowered the er down to 60:40 and also by the basic nitrogen of 3-pyridinecarboxaldehyde also favouring a racemic pathway in the reaction with (*S*)-BINOLAM-AlCl **3** (Table 2, entry 12). A further indirect proof for the intervention of pentacoordinated aluminum species in the above reactions resulted from examination of the (*S*)-BINOL-AlX catalysed cyanation of benzaldehyde. In a previous work published by Nakai et al. the in situ formed dicyanotitanium(IV) complex **11** was predicted as the catalytically active species.[3] By analogy, since both (*S*)-BINOL-AlCN **12** and (*S*)-BINOL-AlCl **5** lack the Brönsted base arm present in the BINOLAM ligand we assumed that catalysis, if occurring, would take place through the standard tetracoordinated species. In agreement with this reasoning we found that, in both cases, benzaldehyde cyanohydrin was obtained in quantitative yield and high enantioselection as revealed by a 95/5 or 96/4 er, respectively. Therefore we tentatively conclude that pentacoordinated aluminum catalysts (LABB catalysts) are more efficient hydrocyanation catalysts than tetracoordinated ones (LA catalysts) alone.



11



12

The absence of a NLE in the reaction catalysed by complexes **5** and **12** also suggest that monomeric species control the process. Thus, the BINOL-AlCN complex **12** would participate as a monofunctional catalytic species in the catalytic cycle through a direct cyanide ion transfer from the aluminium centre in the tetracoordinated complex obtained from compound **12** and the ligated aldehyde, regenerating the active complex after a silylation reaction of the aluminium alcoholate with TMSCN. In order to experimentally justify this hypothesis, ^{27}Al NMR (CD_2Cl_2, 500 MHz) experiments were recorded. The ^{27}Al NMR experiments of BINOL-AlCl **5** and BINOL-AlCN **12** alone and with additives afforded very confusing results, but never with a typical band of pentacoordinated aluminium species at 47 ppm being observed. The ^{31}P NMR spectra of an equivalent amount of BINOL-AlCl complex and triphenylphosphine oxide revealed six different signals at 41.2, 41.5, 42.1, 43.6, 45.3 and 46.3 ppm (free triphenylphosphine oxide 30.1 ppm) corresponding to, at least, six different coordination sites.

In summary, we have shown that the BINOLAM-AlCl catalytic complex is more efficient than the otherwise simpler LA catalyst BINOL-AlCl in the hydrocyanation of aldehydes. The catalyst works as a bifunctional LABB by ligating the carbonyl group to the chiral aluminium, thereby becoming a pentacoordinated chloro-aluminium species. This LABB catalyst has similar efficiency to Shibasaki's LALB phosphine oxide catalyst while allowing reactions to be carried out at higher temperatures and with easier set up. In addition, we have demonstrated that the chiral ligand (*S*)-BINOLAM **3** can be easily and quantitatively recovered at the end of the reaction and recycled, thus suggesting the possible application of this methodology in large-scale processes.

3. Experimental

3.1. General

All reactions were carried out under argon, including the transfer of the solid reagents to the reaction vessel. Anhydrous solvents were freshly distilled under an argon atmosphere and aldehydes were also distilled prior to use. Molecular sieves were treated at 120 °C for 4 h. (*S*)- and (*R*)-BINOLAM were prepared according to the literature protocol.[9–12] 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 important peaks are listed. NMR spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a Shimadzu LC-10AD equipped with the corresponding chiral column (Chiralcel OD-H and Chiralpack AD and AS) described for each compound, using mixtures of n-hexane/isopropyl alcohol as mobile phase. Chiral GC analysis was performed on a HP-5890 using a WCOT γ-cyclodextrin column. 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 and Schuell F1400/LS silica gel plates and the spots were visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm).

3.2. General procedure for the enantioselective synthesis of cyanohydrins 4 mediated by (*S*)- or (*R*)-BINOLAM-AlCl or by (*S*)-BINOL-AlCl

To a suspension of enantiopure (*S*)- or (*R*)-BINOLAM **2**[12]

or (*S*)- or (*R*)-BINOL (0.025 mmol), triphenylphosphine oxide (0.1 mmol, 28 mg) and 4 Å molecular sieves (previously dried at 120 °C for 4 h) in dry toluene (1 mL), under an inert atmosphere (argon), was added dimethylaluminium chloride (1 M solution in hexanes, 0.025 mmol, 25 μL). The resulting suspension was then stirred at room temperature for 1 h. This mixture was cooled at −20 or −40 °C (see Table 2) and then freshly distilled aldehyde (0.25 mmol) and TMSCN (0.75 mmol, 100 μL) were added in one portion. The reaction was monitored by ^{1}H NMR spectroscopy and when it was judged complete a 2 M aqueous solution of hydrochloric acid (2 mL) and ethyl acetate (2 mL) were added, stirring vigorously the resulting mixture for 1 h. The emulsion was filtered trough a celite pad and the organic layer was separated, dried ($MgSO_4$) and evaporated, affording a residue which was purified by flash chromatography obtaining pure cyanohydrins **4**. These compounds were derivatised for chiral HPLC analysis by treatment with 3 equiv. of the base in dry dichloromethane and 1.2 equiv. of the corresponding chloride (AcCl/pyridine, TBDMSCl/imidazole/DMAP(cat), BzCl/triethylamine or MeOCOCl/triethylamine) overnight at room temperature. Yields, enantiomeric ratios and other conditions are given in Tables 1–4. The retention time of the major enantiomer is given in bold. The physical and spectroscopic data for compounds **4** follow:

3.2.1. (*R*)-Mandelonitrile (4a).[32] Colorless oil; $[\alpha]_D^{25}=+42.2$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[3] $[\alpha]_D^{25}=+36.8$ (*c* 2, $CHCl_3$, 85% ee)]; IR (film) ν_{max}: 3222 and 2249 cm^{-1}; ^{1}H NMR δ_H: 3.18 (br. s, 1H), 5.53 (s, 1H), 7.42–7.45 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR δ_C: 63.6, 118.7, 126.6, 129.2, 129.8, 135.0; MS (EI) *m/z*: 107 (M^+-26, 8%), 106 (78), 105 (88), 77 (100), 51 (74); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **11.0** and 14.0 min for the *O*-acetylcyanohydrin.

3.2.2. (*R*)-2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (4b).[34] Colorless oil; $[\alpha]_D^{25}=+40.7$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+36.3$ (*c* 0.97, $CHCl_3$, 83% ee)]; IR (film) ν_{max}: 3420 and 2249 cm^{-1}; ^{1}H NMR δ_H: 3.65 (br. s, 1H), 3.81 (s, 3H), 5.46 (s, 1H), 6.93 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=8.7$ Hz, 2H); ^{13}C NMR δ_C: 55.3, 63.1, 114.4, 119.0, 127.6, 128.2, 160.4; MS (EI) *m/z*: 161 (M^+-2, 1%), 145 (3), 135 (100), 107 (13), 92 (15), 77 (40); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **11.2** and 12.6 min for the *O*-acetylcyanohydrin.

3.2.3. (*R*)-2-Hydroxy-2-[4-(*N*,*N*-dimethylamino)phenyl]-acetonitrile (4c). Pale yellow prisms, mp 105–106 °C (from *n*-hexane/ethyl acetate); $[\alpha]_D^{25}=+83.3$ *c* 0.6, $CHCl_3$, 98% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+45.1$, $CHCl_3$, 53% ee)]. IR (film) ν_{max}: 3432 and 2244 cm^{-1}; ^{1}H NMR δ_H: 2.56 (br. s, 1H), 2.99 (s, 6H), 5.43 (s, 1H), 6.75 (d, $J=8.8$ Hz, 2H), 7.39 (d, $J=8.8$ Hz, 2H); ^{13}C NMR δ_C: 40.36, 63.31, 112.45, 119.31, 123.05, 127.97, 151.16; MS (EI) *m/z*: 14 (M^+-27, 84%), 148 (100), 132 (14), 77 (22), 51 (13); HRMS calcd. for $C_{10}H_{12}N_2O$: 176.2194, found: 176.2198. HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=6.7$ and **7.2** min for the *O*-TMS-cyanohydrin.

3.2.4. (*S*)-2-(2-Chlorophenyl)-2-hydroxyacetonitrile (4d). Colorless oil; $[\alpha]_D^{25}=-7.0$ (*c* 0.77, $CHCl_3$, 96% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=-2.5$, for the (*R*) enantiomer (*c* 2.9, $CHCl_3$, 67% ee)]; IR (film) ν_{max}: 3409 and 2253 cm^{-1}; ^{1}H NMR δ_H: 3.82 (br. s, 1H), 5.86 (s, 1H), 7.36–7.44 (m, 3H), 7.69–7.73 (m, 1H); ^{13}C NMR δ_C: 60.8, 117.9, 127.6, 128.3, 130.0, 131.0, 132.6, 132.8; MS (EI) *m/z*: 143 (M^+-14, 2%), 139 (100), 111 (41), 75 (26), 51 (18); HRMS calcd. for C_8H_6NOCl: 167.5961, found: 167.5959. HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=7.9$ and **9.2** min for the *O*-acetylcyanohydrin.

3.2.5. (*R*)-2-(4-Chlorophenyl)-2-hydroxyacetonitrile (4e).[32] Colorless oil; $[\alpha]_D^{25}=+31.2$ (*c* 0.8, $CHCl_3$, 98% ee from HPLC) [lit.[32,33] $[\alpha]_D^{25}=+27.2$ (*c* 1.48, $CHCl_3$, 66% ee)]; IR (film) ν_{max}: 3411 and 2252 cm^{-1}; ^{1}H NMR δ_H: 3.89 (br. s, 1H), 5.54 (s, 1H), 7.41–7.50 (m, 4H); ^{13}C NMR δ_C: 62.8, 118.4, 127.9, 129.3, 133.6, 135.9; MS (EI) *m/z*: 163 (M^+, 4%), 139 (75), 111 (37), 75 (25), 49 (13); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **12.8** and 14.5 min for the *O*-acetylcyanohydrin.

3.2.6. (*R*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (4f).[35] Colorless oil; $[\alpha]_D^{25}=+12.9$ (*c* 1, $CHCl_3$, 78% ee from HPLC); [lit.[33] $[\alpha]_D^{25}=+14.0$ (*c* 0.83, $CHCl_3$, 79% ee)]; IR (film) ν_{max}: 3414 and 2251 cm^{-1}; ^{1}H NMR δ_H: 2.78 (br. s, 1H), 5.51 (s, 1H), 7.02–7.42 (m, 9H); ^{13}C NMR δ_C: 63.2, 116.6, 118.5, 119.3, 119.6, 120.9, 123.9, 129.9, 130.6, 137.0, 156.3, 158.1; MS (EI) *m/z*: 199 (M^+-26, 13%), 198 (100), 169 (55), 141 (49), 115 (29), 77 (52); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 90/10, 1.0 mL/min, $t_r=14.0$ and **20.4** min for the *O*-acetylcyanohydrin.

3.2.7. (*S*)-2-Hydroxy-2-(3,4-methylenedioxyphenyl)-acetonitrile (4g).[36] Colorless oil; $[\alpha]_D^{25}=-41.7$ (*c* 1, $CHCl_3$, 94% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+40.8$, (*R*) enantiomer (*c* 1.1; $CHCl_3$, 73% ee)]; IR (film) ν_{max}: 3454 and 2239 cm^{-1}; ^{1}H NMR δ_H: 3.07 (br. s, 1H), 5.43 (s, 1H), 6.00 (s, 2H), 6.81–6.84 (m, 1H), 7.01–7.12 (m, 2H); ^{13}C NMR δ_C: 63.4, 101.6, 107.2, 108.6, 118.7, 120.7, 128.8, 143.3, 143.8; MS (EI) *m/z*: 151 (M^+-26, 8%), 150 (84), 149 (100), 121 (31), 91 (10), 63 (26); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=16.1$ and **18.2** min for the *O*-acetylcyanohydrin.

3.2.8. (*R*)-2-Hydroxy-2-(6-methoxynaphthalen-2-yl)-acetonitrile (4h).[36] Pale yellow needles, mp 113–114 °C (from *n*-hexane/ethyl acetate); $[\alpha]_D^{25}=+24.0$ (*c* 0.9, $CHCl_3$) (90% ee from HPLC); IR (KBr) ν_{max}: 3439 and 2240 cm^{-1}; ^{1}H NMR δ_H: 3.91 (s, 3H), 4.81 (br. s, 1H), 5.89 (s, 1H), 7.19 (dd, $J=2.4$, 8.9 Hz, 1H), 7.32 (d, $J=2.3$ Hz, 1H), 7.61 (m, 1H), 7.87 (m, 2H), 7.98 (s, 1H); ^{13}C NMR (d_6-DMSO) δ_C: 55.6, 63.5, 106.6, 120.2, 120.7, 125.4, 126.3, 128.4, 129.3, 130.4, 133.1, 135.8, 159.3; MS (EI) *m/z*: 186 (M^+-27, 100%), 157 (38), 115 (41); HRMS calcd. for $C_{13}H_{11}NO_2$: 187.0759, found: 187.0739; Microanalyses required for $C_{13}H_{11}NO_2$: C, 72.0%; H, 5.1%; N, 6.3%; found: C, 73.2%; H, 5.2%; N, 6.5%; HPLC: Daicel Chiralcel OD-H,

$\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **22.3** and 26.4 min for the *O*-acetylcyanohydrin.

3.2.9. (*S*)-2-Hydroxy-2-(3-pyridinyl)acetonitrile (4i).[37] Pale yellow oil; $[\alpha]_D^{25}=-22.1$ (*c* 1$CHCl_3$) (50% ee from HPLC) [lit.[37] $[\alpha]_D^{25}=+21.4$, (*R*) enantiomer (*c* 0.95, $CHCl_3$) 50% ee)]; IR (film) ν_{max}: 3429 and 2239 cm^{-1}; ^1H NMR δ_H: 5.53 (br. s, 1H), 5.65 (s, 1H), 7.34 (dd, $J=4.8$, 7.9 Hz, 1H), 7.82 (d, $J=7.9$ Hz, 1H), 8.61 (d, $J=4.8$ Hz, 1H), 8.66 (s, 1H); ^{13}C NMR δ_C: 61.5, 118.9, 123.7, 132.2, 134.1, 147.6, 150.4; MS (EI) *m/z*: 108 (M^+-26, 4%), 84 (100); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=12.1$ and **15.3** min. for the *O*-trimethylsilyl cyanohydrin.

3.2.10. (*S*)-2-(2-Furyl)-2-hydroxyacetonitrile (4j).[38] Colorless oil; $[\alpha]_D^{25}=+45.6$ (*c* 0.8, $CHCl_3$, 92% ee from HPLC) [lit[38] $[\alpha]_D^{25}=+50.3$ (*c* 1.6, $CHCl_3$, 99% ee)]; IR (film) ν_{max}: 3270 and 2258 cm^{-1}; ^1H NMR δ_H: 2.98 (br. s, 1H), 5.54 (s, 1H), 6.43 (dd, $J=3.0$, 1.9 Hz, 1H), 6.60 (d, $J=$ 3.0 Hz, 1H), 7.49 (d, $J=1.9$ Hz, 1H); ^{13}C NMR δ_C: 60.7, 109.9, 110.8, 117.0, 144.2, 148.5; MS (EI) *m/z*: 106 (M^+- 17, 1%), 96 (100); HPLC: Daicel Chiralpak AS, $\lambda=254$ nm, *n*-hexane/2-propanol 95/5, 1.0 mL/min, $t_r=21.0$ and **28.9** min for the *O*-acetylcyanohydrin.

3.2.11. (2*R*,3*E*)-2-(Methoxycarbonyloxy)-3-nonenenitrile (*O*-methoxycarbonyl-4k). Colorless oil; $[\alpha]_D^{25}=-14.4$ (*c* 2.0, $CHCl_3$, 96% ee from HPLC); IR (film) ν_{max}: 2249 and 1763 cm^{-1}; ^1H NMR δ_H: 0.89 (t, $J=6.7$ Hz, 3H), 1.25–1.30 (m, 4H), 1.40–1.45 (m, 2H), 2.13 (m, 2H), 3.86 (s, 3H), 5.54–5.61 (m, 1H), 5.66–5.68 (m, 1H), 6.19 (dt, $J=14.6$, 7.2 Hz, 1H); ^{13}C NMR δ_C: 13.8, 22.3, 27.8, 31.1, 31.9, 55.6, 65.1, 115.2, 119.4, 141.5, 154.0; MS (EI) *m/z* 211 (M^+, 2%), 154 (34), 136 (22), 120 (31), 106 (38), 93 (46), 80 (99), 69 (57), 55 (100); HRMS calcd. for $C_{11}H_{17}NO_3$: 211.1208, found: 211.1212; HPLC: Daicel Chiralcel OD-H, $\lambda=$ 210 nm, *n*-hexane/2-propanol 95/5, 0.5 mL/min, $t_r=$**9.6** and 10.8 min.

3.2.12. (2*S*,3*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (4l).[39] Colorless oil; $[\alpha]_D^{25}=-22.7$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[33] $[\alpha]_D^{25}=+19.2$, (*R*) enantiomer (*c* 1.9, $CHCl_3$, 72% ee)]; IR (film) ν_{max}: 3413 and 2249 cm^{-1}; ^1H NMR δ_H: 3.65 (br. s, 1H), 5.14 (d, $J=5.9$ Hz, 1H), 6.25 (dd, $J=15.8$, 5.9 Hz, 1H), 6.91 (d, $J=15.8$ Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR δ_C: 61.8, 118.1, 122.3, 127.0, 128.8, 129.0, 134.7, 135.2; MS (EI) *m/z*: 142 (M^+-17, 1%), 131 (100), 103 (53), 77 (39); HPLC: Daicel Chiralpak AS, $\lambda=$ 254 nm, *n*-hexane/2-propanol 99.3/0.7, 1.0 mL/min, $t_r=$ 16.5 and **18.8** min for the *O*-acetylcyanohydrin.

3.2.13. (*S*)-2-Hydroxy-4-phenylbutanenitrile (4m).[6b] Colorless oil; $[\alpha]_D^{25}=+11.3$ (*c* 0.9; $CHCl_3$, 88% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=+6.6$ (*c* 0.68, $CHCl_3$, 97% *ee*)]; IR (film) ν_{max}: 3433 and 2248 cm^{-1}; ^1H NMR δ_H: 2.11–2.19 (m, 2H), 2.83 (t, $J=7.1$ Hz, 2H), 3.55 (br. s, 1H), 4.40 (t, $J=6.7$ Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR δ_C: 30.6, 36.5, 60.3, 119.8, 126.5, 128.4, 128.6, 139.5; MS (EI) *m/z*: 135 (M^+-26, 6%), 134 (63), 105 (33), 91 (100), 78 (45), 65 (17), 51 (22); HPLC: Daicel Chiralcel OD-H, $\lambda=$ 254 nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=8.9$ and **12.2** min for the *O*-TBDMS-cyanohydrin.

3.2.14. (*S*)-2-Hydroxy-*n*-octanenitrile (4n).[6b] Colorless oil; $[\alpha]_D^{25}=-8.0$ (*c* 1.3, $CHCl_3$, 66% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=-13.3$ (*c* 1, $CHCl_3$, 98% *ee*)]; IR (film) ν_{max}: 3327 and 2247 cm^{-1}; ^1H NMR δ_H: 0.9 (t, $J=7.0$ Hz, 3H), 1.22–1.38 (m, 6H), 1.42–1.54 (m, 2H), 1.82–1.88 (m, 2H), 2.19 (br. s, 1H), 4.47 (t, $J=6.7$ Hz, 1H); ^{13}C NMR δ_C: 13.9, 22.4, 24.4, 28.5, 31.5, 36.2, 61.4, 120.0; MS (EI) *m/z*: 141 (M^+, 6%), 129 (11), 114 (19), 101 (28), 75 (40), 55 (100); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99.6/0.4, 0.5 mL/min, $t_r=$**31.8** and 35.6 min for the *O*-benzoylcyanohydrin.

3.2.15. (*S*)-2-Cyclohexyl-2-hydroxyacetonitrile (4o).[39] Pale yellow oil; $[\alpha]_D^{25}=-2.3$ (*c* 2.0, $CHCl_3$, 20% ee from GC) [lit.[39] $[\alpha]_D^{25}=+8.2$, (*R*) enantiomer (*c* 0.77, $CHCl_3$, 79% ee)]; IR (film) ν_{max}: 3441 and 2249 cm^{-1}; ^1H NMR δ_H: 1.07–1.35 (m, 6H), 1.68–1.88 (m, 5H), 3.47 (br. s, 1H), 4.26 (d, $J=6.6$ Hz, 1H); ^{13}C NMR δ_C: 25.8, 27.7, 28.1, 45.7, 66.1, 119.4; MS (EI) *m/z*: 112 (M^+-27, 6%), 94 (18), 83 (46), 68 (27), 55 (100); GC: WCOT γ-CD column (0.25 nm diameter, stationary phase FS-Lipodex-E with a film thick of 0.25 μm), $T_{injector}=250$ °C, $T_{detector}=260$ °C, $T_{column}=$ 90 °C (3 min) and 180 °C (10 °C/min), $P=120$ kPa, $t_r=$ 21.2 and **21.5** min for the *O*-methoxycarbonylcyanohydrin.

3.2.16. Synthesis of (*S*)-2-hydroxy-3-methyl-4-(2-methyl-4-thiazolyl)-3-butenenitrile (4p).[6b] The reaction was performed as described before starting from the aldehyde **6**[6b] adding 9 equiv. of trimethylsilylcyanide in one portion, keeping the reaction at −20 °C for 38 h. The work up and purification methods were done according to the literature[6b] obtaining pure compound **4p** as colorless oil; $[\alpha]_D^{25}=-14.8$ (*c* 0.7, $CHCl_3$, 92% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=-16.5$, (*c* 0.7, $CHCl_3$, 99% ee)]; IR (film) ν_{max}: 3354 and 2346 cm^{-1}; ^1H NMR δ_H: 2.19 (s, 3H), 2.73 (s, 3H), 4.92 (s, 1H), 6.66 (s, 1H), 7.05 (s, 1H); ^{13}C NMR δ_C: 14.3, 19.2, 67.7, 117.7, 118.5, 121.6, 133.9, 151.6, 165.2; *m/z*: 193 (M^+, 1%), 177 (49), 150 (46), 136 (41), 75 (49); HPLC: Daicel Chiralpak AD, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 0.5 mL/min, $t_r=11.2$ and **12.3** min, for the *O*-TBDMS-cyanohydrin.

Acknowledgements

This work has been supported by the DGES of the Spanish Ministerio de Ciencia y Tecnología (BQU2001-0724-C02), by Generalitat Valenciana (CTIOIB/2002/320 and GRUPOS03/134) and by the University of Alicante.

References and notes

1. (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000. (b) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999. (c) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E.; Methods of Organic Chemistry, Stereoselective Synthesis. In *Houben-Weyl*; Theime: Stuttgart/New York, Vol. E21, 1995.
2. For reviews about the asymmetric synthesis of cyanohydrins, see: (a) North, M. *Tetrahedron: Asymmetry* **2003**, *14*,

147–176. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682. (c) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555–1563. (d) North, M. *Synlett* **1993**, 807–820.
3. Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6229–6232.
4. For reviews about bifunctional catalysis, see: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1189–1199. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3–15. (c) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246–5251. (d) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865–1882.
5. (a) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511–524. (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Pharm. Bull.* **2001**, *49*, 511–524.
6. (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642. (b) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805–814.
7. Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650–1652.
8. Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328.
9. For a preliminary communication, see: Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589–2592.
10. Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197–200.
11. Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143–3146.
12. The diethylamino substituted (*S*)- and (*R*)-BINOLAM 2 were used as phase-transfer catalysts for the enantioselective alkylation of the aldimine-Schiff bases of alanine esters: Casas, J.; Nájera, C.; Sansano, J. M.; González, J.; Saá, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699–702. And for the addition of diethylzinc to aldehydes see: Kitajima, H.; Iti, K.; Katsuki, T. *Chem. Lett.* **1996**, 343–344.
13. The influence of Ph_3PO to prevent oligomerisation of the catalyst and to activate trimethylsilyl cyanide has been pointed out byVogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577.
14. The role of molecular sieves 4 Å as H_2O donor has been demonstrated for the case of binaphthol-derived titanium complexes: Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281–282.
15. Vogl, M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1570–1577.
16. Shimizu, M.; Ogawa, T.; Nishi, T. *Tetrahedron Lett.* **2001**, *42*, 5463–5466.
17. Ling, S.-K.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2002**, *65*, 131–135.
18. Cho, B. T.; Kang, S. K.; Shin, S. H. *Tetrahedron: Asymmetry* **2002**, *13*, 1209–1217.
19. Fadnavis, N. W.; Babu, R. L.; Sheehe, G.; Deshpande, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1695–1699.
20. Tolman, C. A.; Parshall, G. W. *J. Chem. Educ.* **1999**, *76*, 178–189.
21. (a) Beckmann, M.; Haack, K.-J. *Chem. Unserer Zeit.* **2003**, *37*, 88–97. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.
22. van Langen, L. M.; van Rantwijk, F.; Sheldon, R. A. *Org. Process Res. Devel.* **2003**, *7*, 828–831.
23. Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Devel.* **2003**, *7*, 285–288.
24. Johnson, D. V.; Felfer, U.; Griengl, H. *Tetrahedron* **2000**, *56*, 781–790.
25. Johnson, D. V.; Griengl, H. *Tetrahedron* **1997**, *53*, 617–624.
26. (a) Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V.; Scarpelli, R.; Pereira, M. M. A.; Bollbuck, B.; Bigot, A.; Werschkun, B.; Winssinger, N. *Chem. Eur. J.* **2000**, *6*, 2783–2800. (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410–6424.
27. (a) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209–213. (b) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *43*, 10521–10532.
28. For some recent reviews of NLE see: (a) Kagan, H. B. *Adv. Synth. Catal.* **2001**, *343*, 227–233. (b) Kagan, H. B. *Synlett* **2001**, 888–899. (c) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382–390. (d) Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495–499.
29. Mason, M. R.; Smidth, J. M.; Bott, S. G.; Barron, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 4971–4984.
30. (a) Zhong, Z.; Dijkstra, P. J.; Feijen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4511–4513. (b) Atwood, D. A.; Harvey, M. J. *Chem. Rev.* **2001**, *101*, 37–52.
31. Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321–1329.
32. Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702–2704.
33. Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522.
34. Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, *41*, 1697–1709.
35. Brown, R. F. C.; Donohue, A. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron* **1994**, *50*, 13739–13752.
36. Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181–185.
37. Chen, P.; Han, S.; Lin, G.; Huang, H.; Li, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 3273–3279.
38. Ziegler, T.; Horsch, B.; Effenberger, F. *Synthesis* **1990**, 575–578.
39. Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H.; Maruoka, K. *Tetrahedron* **2001**, *57*, 867–873.