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Enantioselective cyanoformylation of aldehydes mediated by BINOLAM–AlCl as a monometallic bifunctional catalyst

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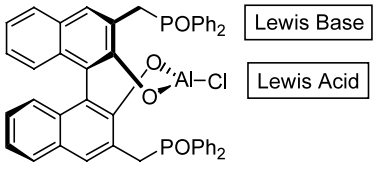
Abstract—BINOLAM–AlCl's, binaphthoxide aluminium chloride species generated in situ from either (*R*)- or (*S*)-3,3′-bis(diethylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthalene (BINOLAM) behave as Lewis acid–Lewis base (LA-LB) catalysts in the enantioselective addition of methyl cyanoformate to aldehydes at room temperature, thereby leading to the asymmetric synthesis of (*S*)- or (*R*)-*O*-methoxycarbonyl cyanohydrins, respectively.

Asymmetric catalysis, based on chiral bifunctional catalysts is a conceptually relevant new strategy for enantioselective synthesis.[1,2] These catalysts bear two non-annihilating centres capable of acting as Lewis or Brönsted acid or base, in order to activate both electrophilic and nucleophilic reagents simultaneously. Shibasaki et al.[2a–c] have recently developed a C_2 symmetric, monometallic, bifunctional Lewis acid–Lewis base (LA-LB) catalysts **1**, derived from 3,3′-diphenylphosphane oxide-substituted BINOL (2,2′-dihydroxy-1,1′-binaphthalene) attached to an aluminium atom. According to Shibasaki, in this system the aluminium atom acts as Lewis acid while the diphenylphosphane oxide arm works as Lewis base activating the electrophile and the nucleophile, respectively. These catalysts have been proved to be highly efficient for the enantioselective addition of trimethylsilyl cyanide to aldehydes,[3] or imines (Strecker reaction),[4] as well as to quinolines and isoquinolines (Reissert-type reaction).[5] On our side, we have recently found that (*S*)- or (*R*)-3,3′-bis(diethylaminomethyl)-1,1′-bi-2-naphthol (BINOLAM) **2** form aluminium complexes **3**, which are efficient catalysts for the enantioselective addition of trimethylsilyl cyanide to aldehydes at −20 to −40°C in the presence of triphenylphosphine oxide and wet 4 Å molecular sieves as additives.[6] While the precise role of the amino group of our catalysts in this reaction (either as Lewis or Bronsted base) is still under study, the aluminium centre worked as Lewis acid. As an additional bonus, we showed that the chiral ligand BINOLAM could be recycled after recovery by simple acid–base extractive work-up.

A much less studied cyanation methodology is the cyanoformylation of carbonyl compounds, which requires a cyanoformate as reagent and tri-*n*-butyltin cyanide as catalyst,[7] or either organic[8] or inorganic bases.[9] The first enantioselective cyanoformylation of ketones (only) has recently been reported by Tian and Deng for which purpose they employ *Cinchona* alkaloid-derived tertiary amines as chiral catalysts.[10] During the preparation of this manuscript, the first asymmetric cyanoformylation of aldehydes with ethyl cyanoformate has been described by Shibasaki et al.[11] The reaction is best performed with a sophisticated catalyst derived from the



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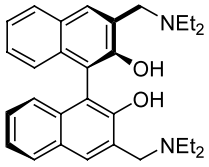
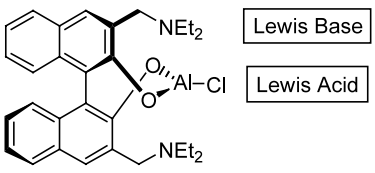


(*R*)-2



(*R*)-3

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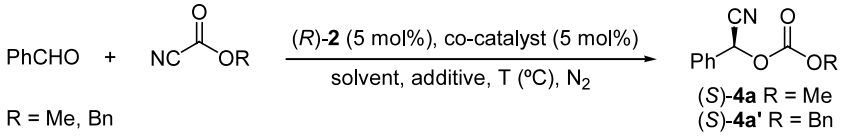
ytrium heterobimetallic complex [YLi_3\{tris(binaphthoxide)\}] (10 mol%) in the presence of water (30 mol%), tris(2,6-dimethoxyphenyl)phosphane oxide (10 mol%) and butyllithium (10 mol%) in THF at −78°C. Herein, we described the use of BINOLAM–AlCl species **3**, derived in situ from (*R*)- and (*S*)-**2**, as efficient monometallic, bifunctional catalysts for the enantioselective cyanoformylation of aldehydes.

Initially we examined the cyanoformylation reaction (Scheme 1) of benzaldehyde and benzyl cyanoformate (1.5 equiv.) at room temperature in dry toluene as solvent, without and with metal-containing co-catalysts (Table 1, entries 1–6). The addition reaction completely failed in the presence of (*R*)-BINOLAM as the only catalyst. Next, titanium and aluminium co-catalysts (Table 1, entries 2–6) were tested, best enantiomeric ratios (*er*) being found when in situ preparing catalyst **3** by mixing (*R*)-BINOLAM with dimethylaluminium chloride (entry 6). Initial results were encouraging though we recognised two major problems to overcome: The appearance of secondary products (mainly benzyl alcohol) presumably derived from competing reactions and the long reaction times (probably caused by a poor turnover step). The first of them was solved using methyl cyanoformate, in which case the crude reaction product could be obtained in high purity (Table 1, entry 7). The long reaction times required were somewhat reduced by employing 4 Å molecular sieves (50 mg/0.25 mmol of aldehyde containing a 7.5% of water) (Table 1, entry 8). The beneficial effect of using molecular sieves in organic reactions is, in most cases, obscure, but in the literature, these effects have been ascribed to their capacity to liberate a certain amount of water into the reaction medium.[12] Other additives such as triphenylphosphane oxide were examined but did not lead to further improvement of the enantiomeric ratio such as was observed in the cyanosilylation of aldehydes.[6,13] The use of toluene and dichloromethane (Table 1, entries 8 and 9) gave similar *er*, the former being selected as the optimal solvent due to the marginally better chemical yield obtained. THF, however, was found to be inappropriate as solvent for this reaction (Table 1, entry 10). Interestingly, the use of lower or higher temperatures did not induce a dramatic change in the enantioselectivity of the process, but only a substantial modification in the reaction rate. On the stereochemical side-walk we found that, in all cases, working with the (*R*)-configured aluminium complex **3** as catalyst, the absolute configuration of carbonate **4a** was *S*. Absolute configurations were unambiguously determined by comparison with pure examples by reaction of enantiomerically pure cyanohydrins[6] with methyl chloroformate in dichloromethane. As expected, enantiomerically enriched carbonates (*R*)-**4** were prepared in identical chemical yield and enantiomeric purity starting from (*S*)-BINOLAM aluminium complex **3**.

We next explored the scope of this reaction under the optimised conditions shown in entry 8 (Table 1). Aldehydes reacted smoothly with methyl cyanoformate (1.5–4 equiv.) in the presence of (*R*)-BINOLAM–AlCl (10 mol%) and 4 Å molecular sieves in dry toluene at room temperature obtaining *O*-methoxycarbonylcyanohydrins **4** in high yields and good enantiomeric ratios (Scheme 2

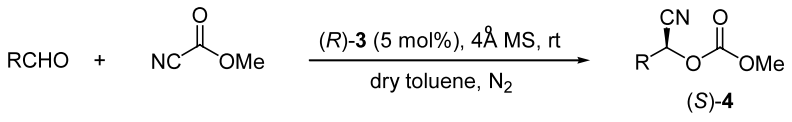


Scheme 1.

Table 1. Optimisation of the reaction conditions for the synthesis of *O*-formylated cyanohydrins **4a** and **4a′**

Entry	R	Co-catalyst	Additive	Solvent	T (°C)	Time (h)	Yield (%)[a]	*er*[b]
1	Bn	–	–	Toluene	25	96	–	–
2	Bn	$Ti(OPr^i)_4$	–	Toluene	25	24	91	63:37
3	Bn	$Ti(OPr^i)_2Cl_2$	–	Toluene	25	48	–	–
4	Bn	Me_3Al	–	Toluene	25	3	>95	50:50
5	Bn	Me_2AlCl	–	Toluene	25	48	53	88:12
6	Bn	Et_2AlCN	–	Toluene	25	5	>95	56:44
7	Me	Me_2AlCl	–	Toluene	25	72	94	89:11
8	Me	Me_2AlCl	4 Å MS	Toluene	25	28	94	89:11
9	Me	Me_2AlCl	4 Å MS	CH_2Cl_2	25	28	87	89:11
10	Me	Me_2AlCl	4 Å MS	THF	25	44	80	76:24

[a] Isolated yield of pure crude compounds determined by ^1H NMR.
[b] Determined by chiral HPLC (Daicel Chiralcel OD-H).



Scheme 2.

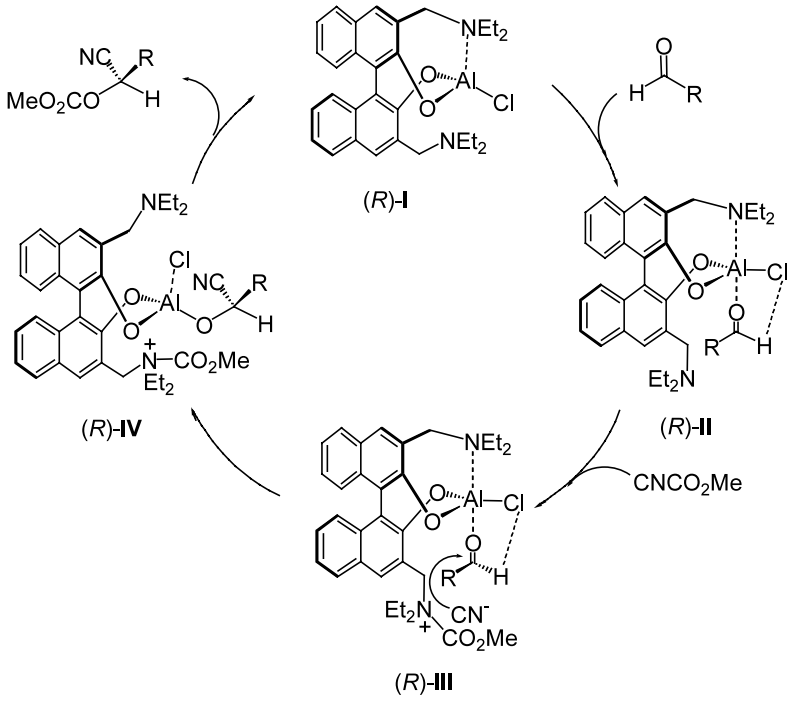
and Table 2). Aromatic aldehydes reacted in almost quantitative yields to give the protected cyanohydrins with up to 78% e.e. However, the reaction of heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde took place in high chemical yield but, unfortunately, with no enantioselection, (Table 2, entry 5), probably because in this case the racemic cycle, where the pyridine nitrogen atom act as a base in activating methyl cyanoformate, predominates. Conjugated and aliphatic aldehydes (Table 2, entries 6–10) also gave good enantiomeric ratios, 3-methylbut-2-enal being a suitable substrate for this reaction (82% e.e.). Surprisingly, no reaction was observed with ketones using the bifunctional catalyst **3** or the chiral basic ligand **2**, under the typical reaction conditions or even when working at higher temperatures. This a priori unexpected result, in light of the report of Deng et al.,[10] is however an indirect evidence for the dual mechanistic role our catalyst must play (see below). As described previously, ligand **2** could be recovered by extractive work-up and subsequently reused without any loss of activity.

The dual LA-LB mechanism (Scheme 3) we assign to the catalyst in this reaction is supported by some experimental studies. Thus, on the one hand, as reported by Deng et al.,[10] chiral tertiary amines working as Lewis bases catalyse the cyanoformylation of ketones only. On the other hand, the use of a tertiary amine-depleted catalyst such as (*S*)-BINOL–AlCl led to no reaction after 2 days at room temperature, thus showing that a Lewis acid alone does not promote the reaction. In our catalyst, the role of the diethylamino group, acting as a

Table 2. Synthesis of cyanoformates **4**[14]

Entry	R	$NCCO_2Me$ (equiv.)	Time (h)	**4**	Yield (%)[a]	*er*[b]
1	Ph	3	28	**4a**	>98	89:11[c,d]
2	4-Cl-C_6H_4	4	24	**4b**	>98	90:10
3	4-MeO-C_6H_4	4	20	**4c**	>98	89:11
4	2-Naphthyl	4	48	**4d**	>98	85:15
5	2-Pyridyl	4	20	**4e**	96	50:50
6	(*E*)-PhCH=CH	4	24	**4f**	95[e]	83:17
7	Me_2C=CH	4	12	**4g**	>98	91:9
8	(*E*)-MeCH=CH	1.5	20	**4h**	>98	77:23
9	$PhCH_2CH_2$	4	20	**4i**	>98	79:21[f]
10	$CH_3(CH_2)_5$	3	20	**4j**	>98	84:16[f]

[a] Isolated yield of pure crude compounds determined by ^{1}H NMR.
[b] Determined by chiral HPLC (Daicel Chiralcel OD-H and Chiralpak AD and AS).
[c] The opposite absolute configuration of compound **4** was obtained employing (*S*)-**3**.
[d] Identical results were observed with recovered ligand **2**.
[e] 500 mg of 4 Å molecular sieves were employed for 0.25 mmol of cinnamaldehyde.
[f] Determined by chiral GC (γ-cyclodextrin).



Scheme 3.

Lewis base and the Al–Cl moiety acting as Lewis acid, is supported by the following facts: (1) only carbonyl compounds capable of coordinating to the Lewis acid centre, i.e. aldehydes but not ketones, do in fact react; (2) the addition of a competing external base such as triethylamine (20 mol%) lowered the *er* down to 65:35, while simultaneously increased the reaction rate (3 h, >99% yield). Accordingly we propose a catalytic cycle where the central aluminium atom might reach pentacoordination[15,16] by amino and carbonyl group ligation to give species **II**–**III**, where, the aldehyde is fixed by a two point interaction: a strong one involving aluminium and one of the electron pairs on the oxygen carbonyl and a weaker one involving the aldehydic proton and the chlorine atom.[17] The activation of methyl cyanoformate by the tertiary amine,[8,10] followed by transfer of the cyanide to the carbonyl group by the *re* face, affords intermediate **IV** allowing final carbonylation of the cyanohydrin to occur. At this point in our studies we have not assigned a clear-cut role to the water-containing molecular sieves other than facilitating the turnover of the catalyst, possibly at the final step of the cycle.

This work reports for the first time the enantioselective cyanation–methoxycarbonylation of aldehydes with a monometallic, bifunctional catalyst using mild reaction conditions. The reactions occur in good chemical yields and high enantioselectivities, the chiral ligand BINOLAM **2** being easily recovered. The thus obtained enantioenriched cyanohydrin carbonates can be exploited in the synthesis of important building blocks for the synthesis of enantiopure 1,2-bifunctional compounds such as β-amino alcohols by reduction with $LiAlH_4$[10] and also in palladium(0)-catalysed allylic substitution in the case of α,β-unsaturated aldehyde derivatives.[18] An exploration of the scope of these applications and mechanistic studies are currently underway.

Acknowledgements

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References

1. (a) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. Houben-Weyl, *Methods of Organic Chemistry*, *Stereoselective Synthesis*; Thieme: Stuttgart/New York, 1996; Vol. E21; (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; (c) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer Verlag: Berlin, 1999; (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987–2012; (e) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York 1994.
2. (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989–1999; (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3–9; (c) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511–524; (d) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865–1882; (e) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246–5251.
3. (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.
4. Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650–1652.
5. (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801–6808.
6. Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589–2592.
7. (a) Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229–6231; (b) Shin, D.-S.; Jung, Y. S.; Kim, J.-J.; Ahn, C. *Bull. Korean Chem. Soc.* **1998**, *19*, 119–120.
8. (a) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995–6003; (b) Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191–7194.
9. Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188–1190.
10. Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.
11. Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636–3638.
12. The role of molecular sieves as an H_2O donor has been demonstrated in the case of binaphthol-derived titanium complexes: Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281–282.
13. The influence of Ph_3PO to prevent oligomerisation of the catalyst and to activate trimethylsilyl cyanide has been pointed out by: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577.
14. **Typical experimental procedure:** To a suspension of enantiopure (*R*)-BINOLAM **2** (0.025 mmol, 11.4 mg) and 4 Å molecular sieves (previously dried at 120°C for 4 h) in dry toluene (1 mL), under an inert atmosphere (nitrogen), was added dimethylaluminium chloride (1 M solution in hexanes, 0.025 mmol, 25 μL) and the resulting suspension was stirred at room temperature for 1 h. To this mixture freshly distilled aldehyde (0.25 mmol) and methyl cyanoformate (see Table 2) were added in one portion. The reaction was monitored by ^1H NMR spectroscopy and GC and when it was judged complete 1 M aqueous solution of hydrochloric acid (2 mL) and ethyl acetate (2 mL) were added and the organic layer was separated, dried ($MgSO_4$) and evaporated, affording the pure crude product **4**.
15. Aoi, T.; Kagoshima, K.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754–5755.
16. The X-ray structure of the pentacoordinate BINOL–AlMe(THF) dimmer complex has been described: Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441–442.
17. Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321–1329.
18. Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191–7194.