COMMUNICATION

Enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral lanthanoid alkoxides

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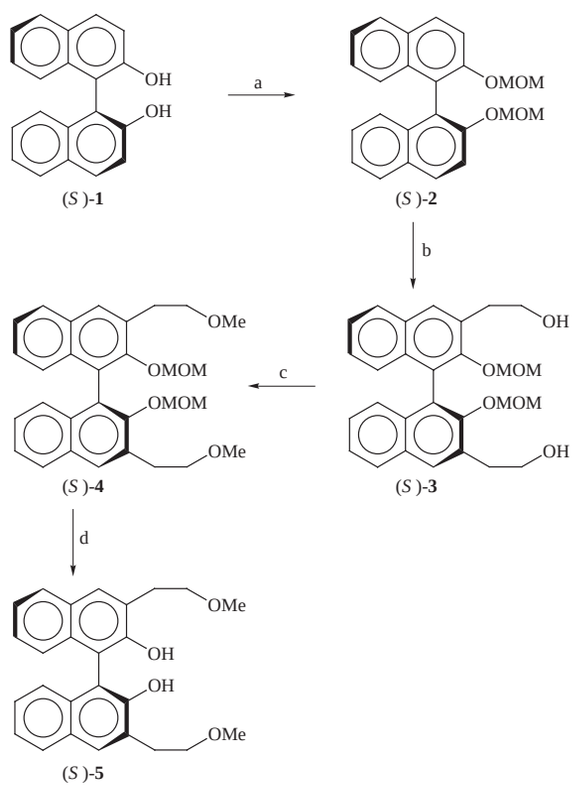
The first example of enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral binaphthol and binaphthol-modified lanthanum alkoxides has been achieved, in which an obvious effect of substituents at the 3,3′-positions of BINOL on the enantioselectivity was observed and 3,3′-bis(methoxyethyl)-BINOL had the advantage over simple BINOL to give (*S*)-products in excellent yields with 73% ee.

Lanthanide reagents have attracted much attention recently because of their potential use in organic synthesis.[1] Especially of interest is their use in catalytic asymmetric reactions. There are a few reports on successful catalytic asymmetric C–C bond forming reactions catalyzed by a lanthanide complex.[2] Optically active cyanohydrins are an important class of versatile intermediates in organic synthesis and hence much effort has currently been directed towards the development of enantioselective catalysts for cyanosilylation of aldehydes.[3] However, to the best of our knowledge, no chiral lanthanide complex has yet been successfully applied to this asymmetric reaction. Here we wish to report the first example of enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral lanthanoid alkoxides.

The readily obtainable (*S*)-BINOL **1**, (*S*)-3,3′-bis(trimethylsilyl)-BINOL,[4] (*S*)-3,3′-diphenyl-BINOL[5] and a new chiral ligand, (*S*)-3,3′-bis(methoxyethyl)-BINOL **5** which we synthesised, were chosen as chiral auxiliaries. (*S*)-3,3′-Bis(methoxyethyl)-BINOL **5** was conveniently synthesized as a colorless solid in a reasonable total yield (36.6%) from (*S*)-BINOL by ring-opening of ethylene oxide with the dilithium salt of **2**, followed by sequential methylation of the hydroxy groups of the resulting ring-opened product (**3**) with MeI, and demethoxymethylation with a trace of HCl (Scheme 1).

Treatment of (*S*)-BINOL with 1.5 equiv. of $La(OBu^t)_3$ in dichloromethane gave a clear solution containing a catalytically active species for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde. The possible structure of the chiral lanthanum catalyst is shown in Scheme 2. However, the enantioselectivity of the catalyst was low. Thus, use of 10 mol% of the catalyst afforded (*S*)-mandelonitrile after 10 h at −78 °C with only 27% ee (88% yield). The presence of a little $La(OBu^t)_3$ in the catalyst system was thought to be mainly responsible for the lower enantioselectivity. In accord with this assumption, a remarkable increase in the enantioselectivity was observed when an improved catalyst preparation procedure[6] was used, which ensured that no trace amounts of $La(OBu^t)_3$ remained. Thus trimethylsilylcyanation of benzaldehyde in the presence of 10 mol% of the improved catalyst gave (*S*)-mandelonitrile in 81% yield with 49% ee. The activity and enantioselectivity of the catalyst could be adjusted for the reaction by tuning the donor or acceptor ability of the solvents used. Tetrahydrofuran gave a racemic product and dichloromethane proved to be the most favourable solvent for the enantioselectivity of the reaction (Table 1).

Trimethylsilylcyanations of several aldehydes were investigated in the presence of the various kinds of chiral ligands and



Scheme 1 Preparation of (*S*)-3,3′-bis(methoxyethyl)-BINOL **5**. *Reagents and conditions:* a: (i) NaH, rt, (ii) $ClCH_2OCH_3$; b: (i) 3 equiv. Bu^nLi, (ii) ethylene oxide; c: NaH, MeI; d: trace HCl, MeOH, 60 °C.

Table 1 The effect of solvents on the enantioselectivity of the asymmetric trimethylsilylcyanation of benzaldehyde[a] (10 mol% catalyst)

Entry	Solvent	Time/h	Yield (%)	ee (%)[b] (confign.[c])
1	CH_2Cl_2	10	88	27[d] (*S*)
2	CH_2Cl_2	10	81	49 (*S*)
3	THF	6	90	0
4	Toluene	10	65	40 (*S*)

[a] At −78 °C. [b] Determined by ^1H NMR of the corresponding MTPA esters. [c] Determined by comparison of optical rotations with literature values.[3b] [d] A little $La(OBu^t)_3$ may be present.

the conditions which had been optimized for the Me_3SiCN addition to benzaldehyde [eqn. (1)]. As summarized in Table 2,

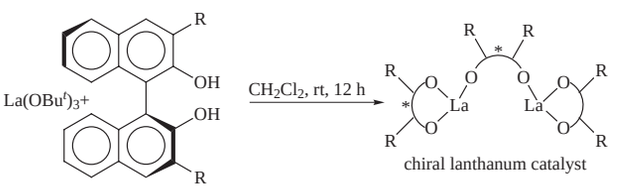
$$RCHO + Me_3SiCN \xrightarrow[CH_2Cl_2,\ -78\ °C,\ 10\ h]{\text{chiral lanthanum catalyst (10 mol\%)}} \underset{R}{\overset{H}{\overset{OH}{\overset{CN}{C}}}} \quad \text{(eqn. 1)}$$

a variety of aldehydes including substituted aromatic and aliphatic aldehydes were silylcyanated in good to excellent yields with modest enantioselectivity. The enantiomeric excesses were determined by ^1H NMR of the corresponding α-methoxy-α-(trifluoromethyl)-phenylacetic esters (MTPA). We found that

Table 2 Enantioselective trimethylsilylcyanation of aldehydes catalyzed by different catalysts

R	Catalyst[a]	Yield (%)	Ee (%)[b] (confign.[c])	R	Catalyst[a]	Yield (%)	Ee (%)[b] (confign.[c])
Ph	I	81	49 (*S*)	$PhCH_2CH_2$	I	82	52 (*S*)
	II	86	36 (*S*)		II	85	27 (*S*)
	III	84	32 (*S*)		III	87	19 (*S*)
	IV	77	71 (*S*)		IV	80	66 (*S*)
p-$CH_3C_6H_4$	I	79	58 (*S*)	*p*-ClC_6H_4	I	83	23 (*S*)
	II	83	40 (*S*)		II	92	7 (*S*)
	III	82	34 (*S*)		III	85	11 (*S*)
	IV	80	73 (*S*)		IV	82	48 (*S*)
p-$CH_3OC_6H_4$	IV	56	63 (*S*)	c-C_6H_{11}	IV	76	54 (*S*)

[a] Catalysts were prepared according to the improved preparation procedure.[6] [b] Ee value was determined by ^{1}H NMR of the corresponding MTPA ester. [c] Absolute configuration determined by comparison of the optical rotation with literature values.[3b,3e]



Catalyst I: R = H
Catalyst II: R = $SiMe_3$
Catalyst III: R = Ph
Catalyst IV: R = $CH_2CH_2OCH_3$

Scheme 2 Preparation of chiral lanthanum catalyst

the substituents of BINOL had a significant effect on the enantioselectivity of the asymmetric trimethylsilylcyanation of aldehydes. This is exemplified by a comparison of catalysts I, II, III and IV. Sterically hindered ligands such as 3,3′-bis(trimethylsilyl)-BINOL and 3,3′-diphenyl-BINOL produced α-hydroxy nitriles with lower enantioselectivity than simple BINOL **1**. As expected, a remarkable increase in the enantioselectivity was achieved when the tetradentate ligand **5**, (*S*)-3,3′-bis(methoxyethyl)-BINOL, was applied. Chiral catalyst IV afforded the products in 48–73% ee, which was higher than that provided by simple BINOL (23–58%). Although the relationship between the substituents of BINOL and the enantioselectivity is not completely clear at present, certain features of the substituents seem to be responsible for the extent of enantioselection. In general, sterically larger 3,3′-substituents of BINOL induced a negative effect on the enantioselectivity of the reaction, which was in sharp contrast with that in the case of main-group and transition metals. We thought that this should be related to the predominant electrostatic interaction between lanthanide ion and ligand, which makes steric factors extremely important in determining the reactivities and structures of lanthanide complexes. Because of the large radius of the lanthanide ion, the enhanced steric hindrance of the ligand would lengthen the M–O bonds of lanthanide oxides, make the asymmetric space looser and as a result lead to reduced asymmetric induction. On the other hand, coordination between the oxygen atoms of *ortho*-substituents and lanthanum ions was beneficial and produced a favorable steric environment and improved the asymmetric induction; furthermore, the coordination bond was indicated by the following two factors in Catalyst IV. (i) C-O-C absorption frequency of substituents in Catalyst IV appeared at 1097 cm^{-1}, which was a shift of 9 cm^{-1} to low wavenumber relative to the corresponding absorption (1106 cm^{-1}) of the ligand; (ii) the ^{1}H NMR signals of methoxy groups of substituents in Catalyst IV appeared at 3.56 ppm, which was 0.16 ppm downfield relative to the corresponding resonance (3.40 ppm) of the ligand.[7]

In summary, we have achieved the first enantioselective trimethylsilylcyanation of aldehydes catalysed by chiral lanthanoid alkoxides. Although the enantioselectivity of the present reaction is modest, an obvious effect of substituents at the 3,3′-position of BINOL on the enantioselectivity was observed. The tetradentate ligand (*S*)-3,3′-bis(methoxyethyl)-BINOL **5** proved to be superior to simple bidentate BINOL to give (*S*)-α-hydroxy nitriles in good yields with higher optical purities (73% ee). Further studies on the asymmetric reaction are now in progress in our research group.

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6 An improved procedure for the preparation of chiral lanthanum catalyst: a solution of (*S*)-BINOL (42.9 mg, 0.15 mmol) in CH_2Cl_2 was mixed with a solution of lanthanum tri-*tert*-butoxide (0.1 mmol) in CH_2Cl_2 under Ar atmosphere in a 25 ml Schlenk flask. The mixture was allowed to stir at room temperature for 12 h to give a yellow solution. In order to remove the resulting Bu^{t}OH completely and ensure that all the lanthanum tri-*tert*-butoxide was consumed, the solvent was removed under vacuum until a dry residue was obtained. After the residue was dried at 50 °C under vacuum for 2 h, the desired product was directly used as an asymmetric catalyst.

Representative procedure for trimethylsilylcyanation of aldehydes: a solution of chiral binaphthol-modified lanthanum alkoxide (0.1 mmol) in dichloromethane (4 ml) was stirred for 30 min. The solution was cooled to −78 °C and aldehyde (1.0 mmol) and trimethylsilyl cyanide (1.2 mmol) were added. After stirring for 10 h at −78 °C the reaction mixture was warmed to room temperature and was quenched with 2 ml saturated aq. NH_4Cl. The aqueous layer was extracted with diethyl ether (3 × 2 ml). The combined organic layers were dried, filtered and concentrated. The residue was treated with 1 M aq. HCl in methanol, stirred for 30 min at room temp. and solvent was removed by rotary evaporation. The adduct was purified by column chromatography on silica gel to afford the pure desired cyanohydrin product.

Enantioselectivities were determined by ^{1}H NMR of the MTPA esters.

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