Eu(III) dithiocarbamate complex and *N*-*p*-tolylsulfonylphenylalanine as a novel chiral catalyst for the asymmetric synthesis of cyanohydrins†

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The use of a new chiral lanthanide complex derived from a europium dithiocarbamate complex and a *N*-tosylated amino acid for the asymmetric synthesis of cyanohydrins is described. In some cases, high enantioselectivities were observed.

The asymmetric syntheses of cyanohydrins have attracted considerable attention due to their synthetic versatility and their utility as chiral starting materials for natural product synthesis.[1] Upon transformation, optically active cyanohydrins can be transformed into the corresponding α-hydroxyacids,[2] α-hydroxyketones,[3] α-amino acids[4] and β-amino alcohols,[5] not only important building blocks in the synthesis of natural products but also in the fields of biology and pharmaceuticals.

A range of catalyst classes are available for this reaction, including enzymes,[6] cyclic dipeptides,[7] chiral Lewis acids[8] and bases[9] and chiral transition metal complexes.[10]

Many enantiomerically pure lanthanide complexes have now been prepared and characterized. One of the first applications of these complexes was as chiral shift reagents for resolving NMR spectra of chiral Lewis bases.[11] More recently, the design of new complexes with applications in asymmetric synthesis has attracted much attention.[12] Moreover the use of complexes derived from lanthanide(III) chlorides,[13] alkoxides,[14] triflates[15] and cyanides[16] for asymmetric cyanation reactions were already reported. We describe herein a highly enantioselective method for cyanation of aromatic aldehydes by the use of europium diethyldithiocarbamate **1**, an inexpensive catalyst, as a precursor for lanthanide chiral catalysts (Fig. 1).

The use of complex **1** has some advantages if compared to other systems: (a) chemical stability and easy manipulation in anhydrous form; (b) the dithiocarbamate ligand can be easily replaced by other oxygen- and/or-nitrogen-containing ligands; (c) the reaction can be easily monitored since the complex **1** is colored and become colorless and luminesces in solution when dithiocarbamate ligand is replaced, because dithiocarbamate anions act as quenchers of Eu(III) luminescence;[17] (d) the complexes are highly soluble in organic solvents.

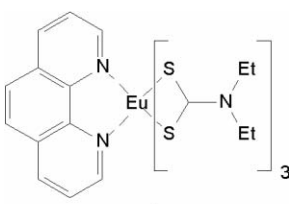

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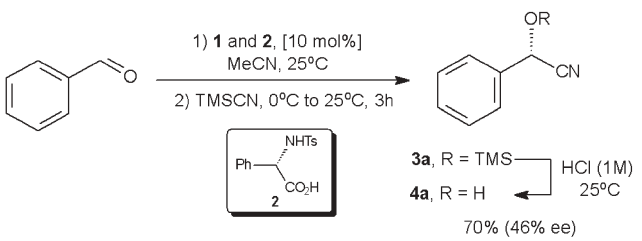
Fig. 1 Eu(III) diethyldithiocarbamate complex **1**.

The *p*-toluenesulfonylamide group in *p*-toluenesulfonylamino acid is able to form intermolecular interactions such as O–H···O, N–H···O and O–H···N, and it can contribute to the formation of strong hydrogen bonds to give supramolecular structures.[18] Recently, X-ray structural analysis of similar lanthanide complexes revealed that the presence of carboxylate bridges with lanthanide ions results in a dinuclear structure.[19]

The first reaction investigated was the conversion of benzaldehyde into the corresponding cyanohydrin with TMSCN using the catalyst prepared *in situ* from a 1 : 1 mixture of dithiocarbamate complex **1** and *N*-*p*-tolylsulfonyl-L-phenylalanine **2**.[20,21] The desired cyanohydrin **4a** was obtained in 46% ee and in good yield (Scheme 1).‡

For this interesting result, we suspected that the ratio of **1** and protected amino acid **2** could give different results regarding the enantiomeric excess and results using a ratios of 1 : 1–3 are shown in Table 1.



Scheme 1

Table 1 Effect of the ratio of europium diethyldithylcarbamate (**1**) to *N*-*p*-tolylsulfonyl-L-phenylalanine (**2**) on the addition of TMSCN to PhCHO

Entry	Ratio **1** : **2**	Yield (%)	Ee[a] (%)
1	1 : 1	70	46
2	1 : 2	72	80
3	1 : 3	85	85

Conditions: Catalyst **1** (10 mol%) and **2** (10–30 mol%), PhCHO : TMSCN (1 : 1.3) The time for complete conversion of PhCHO was 3 h as determined by TLC. [a] Determined by conversion of the obtained cyanohydrin into the corresponding MTPA ester followed by ^{19}F NMR spectroscopy.

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† Electronic supplementary information (ESI) available: Luminescence spectra of solutions of europium dithiocarbamate and 0–3 eqiuvalents of *N*-tosylated amino acid. ^{1}H and ^{13}C NMR spctra of **2**. See DOI: 10.1039/b607741m

Table 2 Effect of the solvent on the addition of TMSCN to PhCHO catalysed by the complex formed between **1** and **2**

Solvent	Time[a]/h	Yield (%)	Ee[b] (%)
CH_3CN	3.0	85	85
CH_2Cl_2	3.5	86	74
THF	3.5	80	72.5
$PhCH_3$	4.0	79	64,5[c]

Conditions: Catalyst **1** (10 mol%) and **2** (30 mol%), ratio 1 : 3, PhCHO : TMSCN (1 : 1.3). [a] The time for complete conversion of PhCHO was determined by TLC. [b] Determined by conversion to the derived MTPA ester as monitored by ^{19}F NMR spectroscopy. [c] Not a homogeneous mixture.

As can be seen in Table 1 using the ratio **1** : **2** has a substantial influence on the enantioselectivity of the obtained product. The optimum ratio was found to be 1 : 3 (Table 1, entry 3). This stoichiometry dependence suggests that the formation of a significant amount of 1 : 3 complex is required to maximize the enantiomeric excess. In the absence of **1**, no reaction was observed and in the absence of the protected amino acid the reaction proceeded over 5 h at room temperature to give the racemic cyanohydrin in 75% isolated yield.

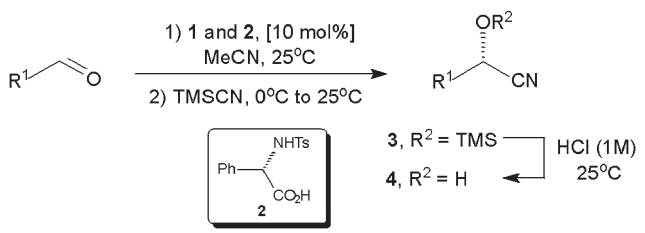
Next, the influence of the solvent in the addition of TMSCN to PhCHO was investigated. The results are shown in Table 2.

We found that the use of acetonitrile as a solvent at room temperature brought about the best results. These conditions were subsequently applied to all other substrates in this study. The results are summarized on Table 3.

As shown in Table 3, the methodology gave the desired cyanohydrins in good yields and in ee's in all cases.

The electronic effects of the aldehyde were briefly studied. All substituted aldehydes proved to have similar reactivities, except for 4-bromobenzaldehyde, giving the desired products in good yields and high ee's (Table 3, compounds **4a–f**). Similar reactivities were observed for both *ortho*- and *para*-substituted aldehydes (Table 3, compounds **4c** and **4d**). When *n*-heptanal was used as the aldehyde source, modest chemical yield and enantioselectivity were observed (Table 3, compound **4g**).

Table 3



Compound	R^1	Time[a]/h	Yield (%)	Ee[b] (%) (confgn.)[c]
4a	C_6H_5	3.0	85	85 (*S*)
4b	Naphthyl	3.0	87	85 (*S*)
4c	4-$NO_2C_6H_4$	1.0	93	99 (*S*)
4d	2-$NO_2C_6H_4$	1.0	90	99 (*S*)
4e	4-$EtOC_6H_4$	3.5	89	89 (*S*)
4f	4-BrC_6H_4	12.0	45	44 (*S*)
4g	*n*-C_6H_{13}	7.0	60	30 (*S*)

Conditions: Catalyst **1** (10 mol%) and **2** (30 mol%), PhCHO : TMSCN (1 : 1.3). [a] The time for complete conversion of RCHO was determined by TLC. [b] Determined by conversion of the obtained cyanohydrin into the corresponding MTPA ester which was monitored by ^{19}F NMR spectroscopy. [c] Configuration assigned by comparison to the literature values of optical rotations.

In summary, we have demonstrated the effectiveness of the use of a new chiral lanthanide complex as chiral Lewis acid in the enantioselective addition of TMSCN to aldehydes. The present methodology shows the first example that uses a europium dithiocarbamate complex as a precursor for a lanthanide chiral catalyst. Furthermore, the reaction was characterized by high enantioselectivities in some cases, low catalyst loading (10 mol%), reasonable tolerance to certain aldehydes and short reaction times. Studies on the mechanism of this reaction as well as the synthesis of other chiral ligands for further applications are currently in progress.

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Notes and references

‡ *Representative procedure*: *N*-tosylated L-phenylalanine **2** (12.24 mg, 0.0384 mmol) was added to a solution of europium diethyldithiocarbamate complex **1** (10 mg, 0.0128 mmol) in acetonitrile (3 mL) under argon at room temperature. The mixture was then stirred for 10 min and the solvent was removed under reduced pressure for withdrawal of dithiocarbamic acid until a dry residue was obtained. The residue was redissolved in acetonitrile (3 mL) and cooled to 0 °C. Benzaldehyde (13 μL, 0.128 mmol) was then added followed by TMSCN (19 μL, 0.152 mmol) and the resulting solution was stirred at room temperature for 3 h before quenching with 1 M HCl (10 mL). The mixture was diluted with dichloromethane (15 mL) and the organic phase was isolated, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel (30% EtOAc–*n*-hexane) to yield 14.5 mg (85%) of the desired compound.

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21 The *N*-tosylated L-phenylalanine was synthesized following a similar route to that described in ref. 20: $[\alpha]_D^{20}$ -7.9^0 (c = 0.015 g mL^{-1} in DMSO), mp 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, 2H), 7.3–7.2 (m, 5H), 7.1 (d, 2H), 6.1 (s, OH), 5.2 (d, 1H), 4.3–4.2 (m, 1H), 3.1 (dd, J = 14, 5.5 Hz, 1H), 3.0 (dd, J = 14, 6.6 Hz, 1H), 2.4 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9, 143.7, 136.7, 134.8, 129.6, 129.4, 128.6, 127.3, 127.1, 56.4, 38.9, 21.4. Anal (%). Calc.: C 60.15, H 5.37, N 4.39. Found: C 58.96, H 5.01, N 4.26.

