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Lanthanide complexes with C_2 symmetric ligands for use in enantioselective organic synthesis

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Abstract

C_2 symmetric chelating ligands can be used to prepare homochiral lanthanide complexes which act as enantioselective reagents and catalysts for synthetically important reactions. [$LnCl_3$(pybox)$_2$] (pybox is 2,6-bis(*substituted*-2-oxazolin-2-yl)pyridine) catalyse the enantioselective silylcyanation of aldehydes. [Li_3Ln(binol)$_3$] (H_2binol is binaphthol) are reagents for the enantioselective addition of MeLi to aldehydes. [La(OTf)$_3$(Pr^i-pybox)$_2$] and [Li(THF)$_2$]$_2$[Li(Et_2O)][Yb(*R*-binol)$_3$] have been characterised by single crystal X-ray diffraction.

Keywords: Lanthanide; Catalysis; Enantioselective; Pybox; Binaphthol

1. Introduction

The lanthanide elements have now become important components of the synthetic organic chemist's armoury. In 1984 organocerium reagents were first recognised as mild and highly selective reagents for alkyl addition to carbonyls [1], and more recently lanthanide triflates Ln(OTf)$_3$ (OTf=CF_3SO_3) have been used as mild and selective Lewis acid catalysts showing high turnover in a range of useful transformations [2]. As well as the practical attractions of relatively low cost, high abundance and low toxicity, the lanthanide elements have chemical features which make them attractive as components of reagents and catalysts for organic synthesis: their oxophilicity combined with lability of the Ln-O bond means that they show mild Lewis acidity combined with rapid dissociation of product after reaction of the substrate. This means that turnover rates can be much higher than for traditional Lewis acids such as BCl_3, where stoichiometric amounts are often required. The large coordination sphere and flexible coordination geometry typical of lanthanide complexes can also be advantageous, allowing coordination of a wide range of substrates and thus being applicable to a potentially wider range of reactions. In addition, the steady decrease in ionic radius on traversing the lanthanide series allows fine-tuning of activity and selectivity of reagents and catalysts.

An important goal for many synthetic organic chemists is the synthesis of enantiomerically pure molecules. Enantioselective catalysis, which requires only a substoichiometric quantity of chiral auxilliary, is especially attractive but requires a catalyst with a well-defined chiral binding site for the substrate. However, features of lanthanide chemistry which enhance reactivity (e.g. labile Ln-to-ligand bonds) make it more difficult to prepare enantioselective catalysts and reagents. In this paper we describe some of our work which has resulted in a highly enantioselective catalyst for cyanohydrin synthesis and a highly enantioselective reagent for methyl addition to aldehydes.

2. Results and discussion

2.1. Enantioselective catalysts for cyanohydrin synthesis

The addition of cyanide ion to aldehydes and ketones generates cyanohydrins. The cyanohydrin functional group is an important tool in synthetic organic chemistry as it can be incorporated intact into complex molecules or may be transformed into a number of other functional groups, e.g. α-amino alcohols, α-chloronitriles, hydroxyaldehydes and acids [3] Except for symmetrical ketones, where R=R′, all

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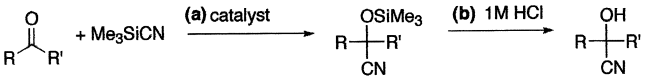
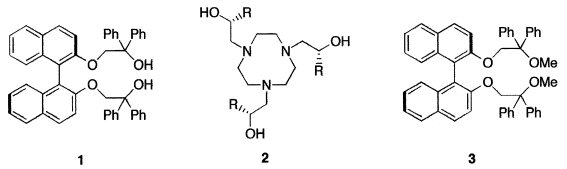
cyanohydrins are chiral, and formation of enantiomerically pure cyanohydrins is an important synthetic goal.

Reaction 1



When we began this work there were a small number of metal-containing enantioselective catalysts for the reaction, based on Ti [4,5] and Sn [6]. Lanthanide complexes had been reported to catalyse silylcyanation of aldehydes and some ketones; these include $LnCl_3$, which is a heterogeneous catalyst [7], and $Yb(CN)_3$ [8]. Acid treatment of the Me_3Si protected product leads to the desired cyanohydrin (reaction 1(b)). Lanthanide(III) alkoxides were reported to catalyse the transhydrocyanation reaction between acetone cyanohydrin and aldehydes [9]. Against this background, we set out to prepare homochiral analogues of these known catalysts.

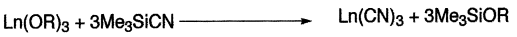
Our first approach was to prepare chiral lanthanide alkoxides using the multidentate alcohols **1** and **2**, and although the silylcyanation reaction was catalysed efficiently by these complexes, the products were racemic.



1 2 3

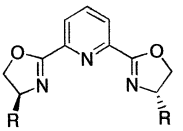
It has been reported that lanthanide alkoxides react with Me_3SiCN to form lanthanide tricyanides and silylated alcohols (reaction 2) [8]. This would explain the lack of enantioselectivity of alkoxide complexes: the chiral alkoxide ligand is being removed by silylation and the resulting $Ln(CN)_3$ is an achiral catalyst for the reaction.

Reaction 2



We then attempted to form chiral complexes of $LnCl_3$ using neutral ligands such as the triglyme analogue **3**. $LnCl_3$ dissolved in THF in the presence of **3** proving that complex formation had occurred, and the resulting solution catalysed the silylcyanation reaction, but gave racemic product. This may be due to **3** binding strongly to $LnCl_3$, but not defining a sufficiently rigid chiral binding site, or it may be caused by **3** not coordinating strongly enough. The latter explanation is more likely as the only crystals isolated from a THF solution of $LnCl_3$ and **3** were identified as $[LnCl_3(THF)_n)]$.

It was clear that chiral alkoxide complexes would be of no use in enantioselective catalysis of the silylcyanation reaction, as the alkoxide ligand was being removed from the Ln by silylation, and that polyether ligands such as **3** did not bind strongly enough to $LnCl_3$ to form a soluble chiral complex. At this point we turned our attention to pybox ligands **4** which have been used successfully in several transition-metal catalysed enantioselective reactions [10].

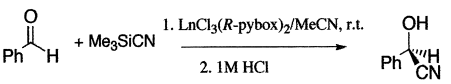


4

These tridentate ligands contain a strong donor pyridine group and were therefore expected to bind strongly to $LnCl_3$, with the rings defining a chiral binding site at the metal.

We found that addition of 1 equivalent of Pr^i_2-pybox to a THF slurry of $PrCl_3$ led to immediate dissolution of some of the $PrCl_3$, demonstrating that complex formation had occurred. The resulting solution catalysed the silylcyanation of PhCHO (10 equivalents): the reaction was complete after 16 h at room temperature and the product was isolated in 81% yield with 21% ee. In the absence of pybox, the reaction took 5 days to reach completion, and in the absence of $PrCl_3$ there was no reaction at all. Further work (^{1}H NMR spectroscopy and FAB mass spectrometry) established that the complex initially formed was $[LnCl_3(Pr^i\text{-pybox})_2]$, although the active catalyst was probably $[Ln(CN)_3(Pr^i\text{-pybox})_2]$. We next investigated the effects of varying solvent, Ln^{3+} radius, and the substituents on the pybox ligand. In general we found that the more polar solvents gave the best enantioselectivities, and MeCN was found overall to be the best. The results of varying Ln radius and Pybox substituent are summarized in Table 1. It is surprising to note that the largest substituent, Bu^t, which might be expected to have the greatest steric influence, in fact gave rise to the lowest enantioselectivities.

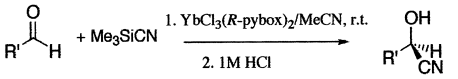
Table 1
Effect of Ln and Pybox substituent on enantioselective hydrocyanation of PhCHO



Ln	R	Time/h	Isolated yield/%	ee/%
Y	Pr^i	1	87	67
Y	Ph	1	77	80
Y	CH_2Ph	1	100	60
La	Pr^i	3	96	12[a]
Eu	Pr^i	16	81	32
Yb	Pr^i	1	94	75
Yb	Ph	0.5	61	89
Yb	Bu^t	3	88	13.8

[a] Reversal of enantioselectivity.

Table 2
Enantioselective silylcyanation catalysed by $YbCl_3(Pr^i_2pybox)_2$



R′CHO	Time/h	Isolated yield	ee/%
Ph-	1	94	75
4-CH_3Ph-	3	93	70
2-furyl-	2	86	67
CH_3-	2	61	45
c-C_6H_{12}-	2	86	60

The best enantioselectivities were obtained with polar solvents (MeCN was the best), the smallest Ln, and with Ph-pybox; the very bulky Bu^t substituent resulted in the worst enantioselectivity. The reaction has now been extended to a wide range of aldehydes with uniformly high isolated yields and ee's obtained under mild and convenient conditions (5 mol% catalyst; 1 h; room temperature) and a representative selection of results with aromatic and aliphatic aldehydes is summarized in Table 2. A preliminary report of this work has been published [11].

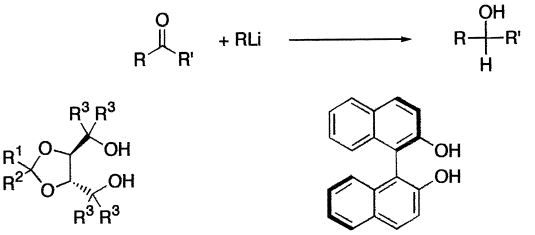
2.2. Structural studies

We have so far been unable to obtain X-ray quality crystals of $[LnCl_3(pybox)_2]$ complexes, however we have characterised the related $[La(OTf)_3(Pr^i\text{-pybox})_2]$ by single crystal X-ray diffraction. (A $Yb(OTf)_3$/pybox system has recently been reported to be an enantioselective catalyst for the cycloaddition of alkenes with nitrones giving ee's of up to 73% [12]) Fig. 1 shows the $[La(Pr^i\text{-pybox})_2]^{3+}$ unit which is expected to be similar to that found in the corresponding $LnCl_3$ complex. This structure shows how two pybox ligands are required to give a reasonably coordinatively saturated, and therefore soluble, complex. The Pr^i groups on a single pybox ligand bound to the large Ln^{3+} ion are much further apart than in a transition metal complex, but the two pybox ligands can cooperate to form a chiral binding site at the metal.

2.3. Enantioselective reagents for Me addition to aldehydes

The enantioselective addition of R to an aldehyde to form an optically pure 2° alcohol (reaction 3) is synthetically important, and it has been found that enantioselective organocerium reagents can be produced in the presence of C_2-symmetric chiral diols such as TADDOL **5** and *R*-binaphthol (*R*-H_2binol) **6** [13–15].

Reaction 3



5 6

In the case of the TADDOL modified reagent, the best enantioselectivities were obtained when 3 equivalents of TADDOL were added for each equivalent of organocerium. This suggested to us that the chiral or-

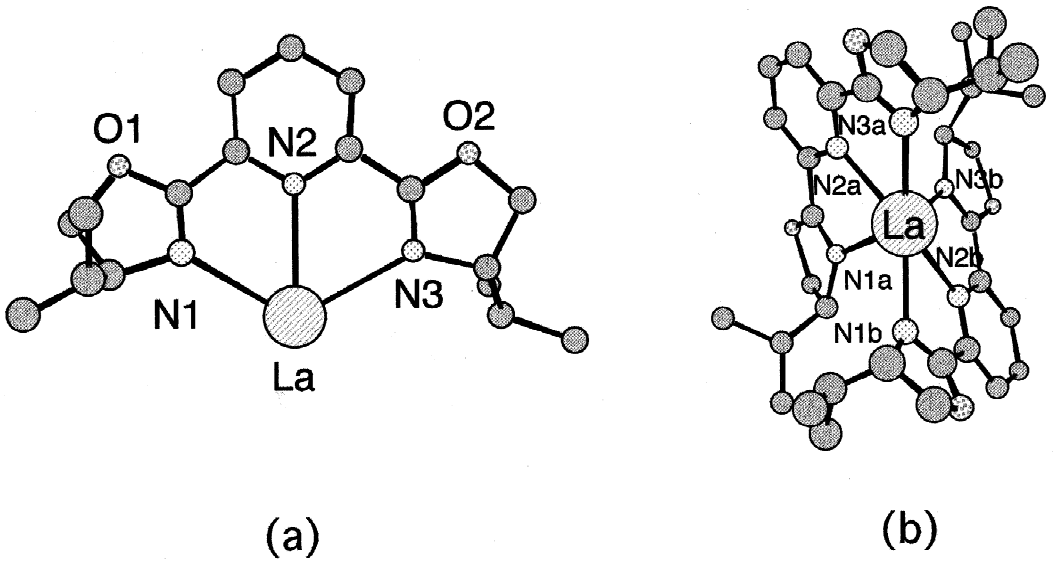
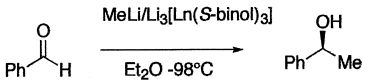


Fig. 1. Crystal structure of $[La(OTf)_3(Pr^i\text{-pybox})_2]$. (a) One pybox ligand bound to La. (b) Two pybox ligands cooperate to form a chiral binding site at La. Selected bond lengths (Å) and angles (deg) are: La-N1, 2.753; La-N2, 2.711; LaN3, 2.686; N1-La-N2, 60.8; N2-La-N3, 60.6; N1-La-N3, 120.9.

Table 3
Effect of Ln on enantioselective methyl addition to PhCHO

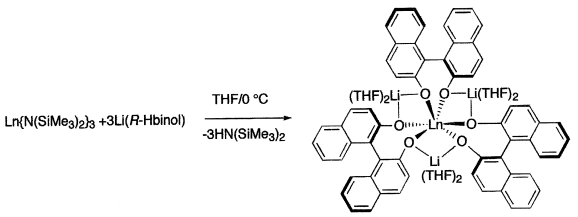


Ln	ee/%
La	84
Y	11
Yb	3

ganocerium reagents might be structurally related to Shibasaki's highly successsful enantioselective mixed metal catalysts $M_3[Ln(binol)_3(H_2O)]$ [16].

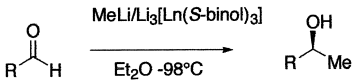
We set out to prepare *anhydrous* complexes which would be compatible with the presence of strongly basic R groups. Reaction of lanthanide *tris*(silylamides) $[Ln\{N(SiMe_3)_2\}_3]$ with 3 equivalents of Li*R*-Hbinol in THF resulted in quantitative formation of $Li_3[Ln(R\text{-binol})_3]$ for Ln = La, Pr, Eu, Y and Yb (reaction 4).

Reaction 4



Alkylating reagents were generated by addition of RLi to a Et_2O solution of $Li_3[Ln(binol)_3]$ at −78°C. After ageing for 1 h at this temperature the reagent was cooled to −98°C and an Et_2O solution of the aldehyde was added over a period of 2 h. The effect of Ln on enantioselectivity was investigated and the results are summarised in Table 3. There is a clear size effect, with La giving the best enantioselelectivity and Yb the worst. A preliminary account of this work has recently been published [17]; the ee's and yields reported in Table 4 are somewhat improved compared with those previously reported. Significantly for the wider utility of these reagents, we have now established that $Li_3[Ln(binol)_3]$ may be handled out on the open bench for brief periods (e.g. for weighing) without any loss of activity: $Li_3[La(S\text{-binol})_3]$ weighed on the open bench gave an ee of 82% in the addition of MeLi to PhCHO.

Table 4
Enantioselective Me addition to aldehydes mediated by $Li_3[La(S\text{-binol})_3]$



RCHO	Isolated yield/%	ee/%
Ph-	46	84
2-naphthyl-	60	67
2-furyl-	31	68
4-tolyl-	87	66

2.4. Structural studies

We have been unable to isolate a sample of the active alkylating agent, which is stable only at low temperatures, but low temperature NMR studies are currently underway inorder to elucidate its solution structure. However, we have characterised $Li_3[Ln(R\text{-binol})_3]$ for Ln = Y or Yb by single crystal X-ray diffraction; crystals of the La complex break down by loss of solvent and so have not been studied. The structure of the Y complex has been published [17]; the Yb complex is similar except that the smaller size of the Yb ion does not allow room for 2 THF ligands to bind to each Li atom, and the overall complex is $[Li(THF)_2]_2[Li(Et_2O)][Yb(R\text{-binol})_3]$. A view of the Yb complex is shown in Fig. 2 along with selected bond lengths and angles.

Although the structure of the active alkylating species is unknown, we do know that $Li_3[La(binol)_3]$ is not simply acting as a chiral Lewis acid to bind aldehyde before subsequent reaction with MeLi: if PhCHO is added first, followed by MeLi, the product is racemic. The first step in the reaction must be formation of a chiral mixed metal organolanthanide species which then transfers Me to PhCHO. Binding of PhCHO to the organolanthanide must occur to allow enantioselective Me transfer, and so Lewis acidity of the reagent is an important property. The organometallic reagents of the later lanthanides probably have insufficient space at the Ln to bind the aldehyde substrate prior to alkyl transfer, leading to much poorer enantioselectivities.

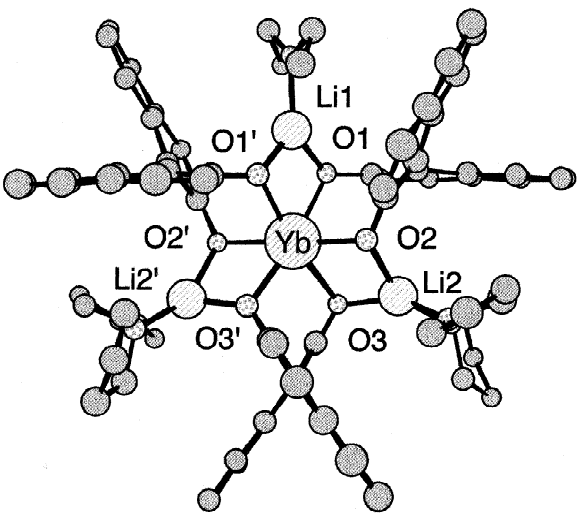


Fig. 2. Crystal structure of $[Li(THF)_2]_2[Li(Et_2O)][Yb(R\text{-binol})_3]$. Selected bond lengths (Å) and angles (deg) are Yb-O1, 2.248; Yb-O2, 2.213; Yb-O3, 2.225; O1-Yb-O1′, 75.5; O1-Yb-O2, 82.6; O2-Yb-O3, 75.4; O3-Yb-O3′, 83.9. O1, O1′, etc. are related by a C_2 rotation through Li1-Yb.

3. Conclusions

We have described two examples of lanthanide catalysts and reagents which may be made enantioselective by the use of C_2 symmetric chelating ligands. The use of strongly binding pybox ligands leads to ligand acceleration of the silylcyanation of aldehydes catalysed by $LnCl_3$, and ee's of up to 89% may be achieved with low catalyst loadings under very mild conditions. Stoichiometric reagents for the enantioselective alkylation of aldehydes can be generated by addition of RLi to $Li_3[Ln(binol)_3]$. In both these classes of reaction the mild Lewis acidity of the Ln^{3+} ion is believed to be an important factor. The ionic radius of Ln^{3+} has a marked effect on the enantioselectivities of the reactions; in the case of the catalytic silylcyanation reaction smaller Ln^{3+} result in improved enantioselectivity; in the alkylation reactions the larger Ln^{3+} give the better results.

Acknowledgements

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