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Catalytic, Asymmetric Cyanohydrin Synthesis Mediated by Lanthanide(III) Chloride Pybox Complexes

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Abstract

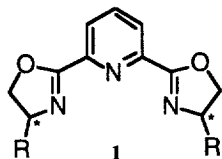
Complexes formed between lanthanide trichlorides and 2,6-bis(*substituted*-2-oxazolin-2-yl)pyridine (pybox) ligands are effective catalysts for the enantioselective addition of trimethylsilylcyanide (TMSCN) to a range of aldehydes. © 1999 Elsevier Science Ltd. All rights reserved.

Key-words Asymmetric synthesis; Catalysis; Cyanohydrins; Lanthanides

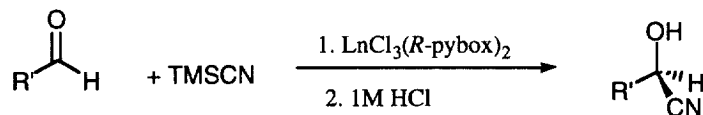
The asymmetric synthesis of cyanohydrins has attracted considerable interest because of the synthetic utility of these compounds, which may be incorporated intact into molecules such as the pyrethroid insecticides cypermethrin and fluvanilate, or readily converted into other intermediates [1, 2]. A number of methods have been reported for the catalytic asymmetric synthesis of cyanohydrins [3]; these may be broadly divided into two categories: enzymatic methods (including the related synthetic peptides), and complexes of metals with chiral ligands. Some recent examples of metal mediated enantioselective cyanohydrin synthesis include the use of Ti complexes [4, 5] and Bi complexes [6]. Salts of the lanthanides (including La and Y as well as the elements Ce to Lu) are typical hard Lewis acids and are finding increasing use as catalysts in organic synthesis. There have been reports of the use of lanthanide(III) alkoxides [7, 8, 9], dialkylamides [10], chlorides [11], cyanides [12] and triflates [13] in the catalysis of the silylcyanation and hydrocyanation of aldehydes and ketones. Since we began our work in the area there have also been reports of the enantioselective silylcyanation of aldehydes catalysed by chiral lanthanide alkoxides [14], and by a chiral complex of SmCl₃ [15]. We now report our work with LnCl₃(pybox)₂ catalysts which resulted in high enantioselectivities after short reaction times at room temperature.

Pybox ligands **1** have been used with great success in enantioselective catalysis by transition metal complexes [16, 17], but when we began this work there were no reports of the use of this class of ligand in lanthanide catalysis [18]. We reasoned that the presence of the

strong donor pyridine group and the potentially tridentate nature of the ligand should lead to stable, soluble complexes, and we began our investigations with PrCl_3 and the commercially available Pr^i -pybox ligand (**1**, $\text{R} = \text{Pr}^i$). Product was isolated in 81% yield and 21% ee [19].



In the absence of PrCl_3 , there was no reaction and in the absence of pybox the reaction proceeded much more slowly (5 days at room temperature) to give racemic product in 73 % isolated yield. The acceleration of the reaction in the presence of pybox can be explained by the formation of a soluble $\text{PrCl}_3/\text{pybox}$ complex: LnCl_3 and their THF adducts are only sparingly soluble in THF.



A substantial increase in ee (to 49%) was obtained for silylcyanation of PhCHO using a $\text{YCl}_3(\text{Pr}^i\text{-pybox})_2$ catalyst system in THF. After this promising result we then investigated the effect of solvent, amount of pybox and nature of pybox on the reaction.

Table 1

Effect of solvent on addition of TMSCN to PhCHO catalysed by $\text{YCl}_3(\text{Pr}^i\text{-pybox})_2$

Solvent	reaction time ^a /h	Isolated Yield/%	ee ^b /%
PhCH_3^c	3	97	26
Et_2O^c	24	85	6
CHCl_3^c	0.5	81	15
THF	3	91	49
CH_2Cl_2^c	3	91	49
CH_3NO_2	3	85	49
CH_3CN	1	88	67
EtOH	24	69	54

Conditions: 10 mol% catalyst, rt, $\text{PhCHO}:\text{TMSCN}$ (1:1.2)

^a Time for complete conversion of PhCHO as determined by TLC

^b Determined by chiral HPLC analysis of TBDMS ether

^c Not a homogeneous mixture

The optimum ratio of $\text{pybox}:\text{LnCl}_3$ was found to be 2:1. The effect of solvent is summarised in Table 1, which shows that in general an increase in solvent polarity leads to an improvement in ee, with the optimum solvent being acetonitrile. In the case of protic solvents such as EtOH the unprotected cyanohydrin is formed directly by addition of HCN generated *in situ* from the reaction of TMSCN with the solvent.

The effects of varying Ln and the substituents on the pybox ligand are summarised in Table 2. Ph-pybox was found to give the best enantioselectivity, although the rate of reaction was found to be slower than with the Prⁱ-pybox. Bu^t-pybox was briefly investigated, but gave substantially lower ee's than other pybox ligands. It is not surprising that there is a variation in enantioselectivity on varying Ln, and thus the radius of Ln³⁺. Of the Ln investigated, YbCl₃ has the smallest ionic radius and shows the best enantioselectivity. More surprising is the observation that LaCl₃ resulted in *reversal* of enantioselectivity.

Table 2

Effect of pybox substituents on addition of TMSCN to PhCHO catalysed by LnCl₃(R-pybox)₂ in MeCN

Ln	R	time/h	isolated yield/%	ee/%
Y	Pr ⁱ	1	87	67
Y	Ph	1	77	80
Y	CH ₂ Ph	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

^a Reversal of enantioselectivity

We have applied our catalytic system to a range of aldehydes; the most comprehensive set of results was obtained using (Prⁱ-pybox)₂YbCl₃, and these are summarised in Table 3. Measurement of optical rotation for cyanohydrins in entries 1, 8 and 9 show that *R* (*S*) stereochemistry in the ligand leads to *R* (*S*) stereochemistry in the product.

The identity of the active catalyst has not been unambiguously established, however (Ph-pybox)₂YbCl₃ has been isolated and characterised (elemental analysis and FAB mass spectrometry), and has been shown to catalyse the addition of TMSCN to PhCHO with the same results as the *in situ* generated catalyst. It is likely that the active catalytic species is a cyanide complex generated by reaction of LnCl₃ with TMSCN.

Table 3

Enantioselective addition of TMSCN to R'CHO using (Prⁱ-pybox)₂YbCl₃ in acetonitrile

Entry	R'CHO	time/h	isolated yield/%	ee/%
1	Ph-	1	94	75
2	3-PhOPh-	2	98	68
3	4-CH ₃ Ph-	3	93	70
4	4-ClPh-	16	60	62
5	2-furyl-	2	86	67
6	CH ₃ -	2	61	45
7	CH ₃ (CH ₂) ₄ -	2	96	46
8	<i>c</i> -C ₆ H ₁₂ -	2	86	60
9	Bu ^t -	2	83	49
10	(<i>E</i>)-hexenal	2	88	58

The combination of the best Ln (Yb), ligand (Ph-pybox) and solvent has achieved an enantioselectivity of 89% for the addition of TMSCN to benzaldehyde in a reaction conducted at room temperature [20]. This is a better enantioselectivity than those reported with other Ln catalysed systems [14, 15] and has been achieved under mild conditions without recourse to low temperatures. Catalytic loadings of less than 10 mol% were not routinely used in this work because of the difficulties in accurate weighing of very small quantities of anhydrous LnCl₃, however some preliminary investigations suggest that catalytic loadings as low as 1 mol% can be used without significant loss of activity. Further investigations of this novel catalytic system are underway and will be reported in due course.

Acknowledgements

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- [19] The catalyst was generated by addition of 1 equiv of pybox to 1 equiv of anhydrous PrCl₃ in THF, resulting in partial dissolution of the PrCl₃. Benzaldehyde (10 equiv) and TMSCN (12 equiv) were added at 0 °C, and after allowing the reaction mixture to warm to room temperature, stirring was continued for 16h, after which TLC showed the reaction to have gone to completion.
- [20] A typical experimental procedure is as follows: Ph-pybox (150 mg, 0.408 mmol) was added to anhydrous YbCl₃ (57 mg, 0.204 mmol) in acetonitrile (10.7 cm³) and stirred at rt for 1h. Benzaldehyde (207 ml, 2.04 mmol) was added and the solution was cooled to 0 °C. TMSCN (327 ml, 2.45 mmol) was added in one portion and the reaction mixture was allowed to warm to rt. After 30 min, 1M aqueous HCl was added and after a few minutes the benzaldehyde cyanohydrin was extracted into Et₂O. This solution was dried (Na₂SO₄) and concentrated under reduced pressure to give the cyanohydrin (166 mg, 61%). This was converted to the *tert*-butyldimethylsilylether [21] and HPLC analysis (Chiracel OD) showed an 89% ee.
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