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Unique Stereocontrol in Europium (III)-Catalyzed Cyanosilylation of Chiral α-Alkoxy and α-Amino Aldehydes

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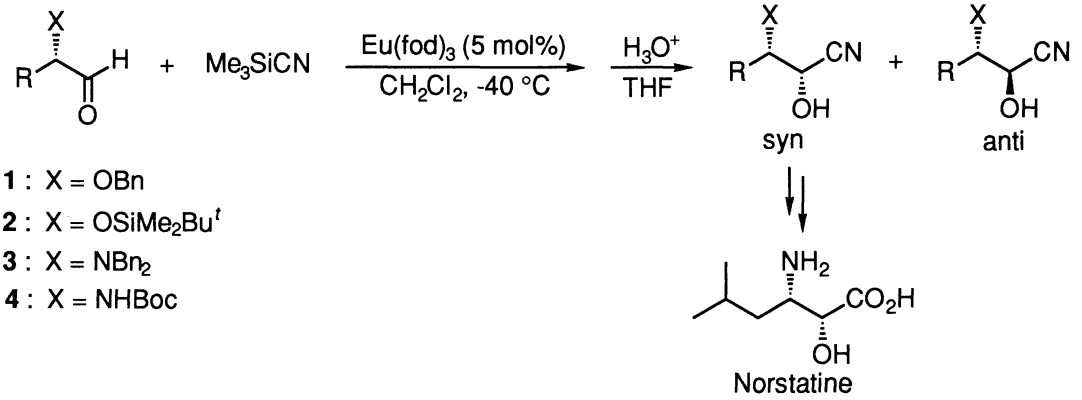
The Eu(III)-catalyzed cyanosilylations of chiral α-alkoxy and α-amino aldehydes are shown to exhibit syn diastereofacial selection, the degree increasing with an increase in steric bulk of the alkyl chain in the aldehydes. The mechanism of this catalytic process is discussed.

Optically active cyanohydrins are an important class of compounds in organic synthesis and hence much effort has currently been directed towards the development of stereoselective catalyst for cyanosilylation of aldehydes.[1] Recently we have reported that europium (III) complexes (NMR shift reagents) provide efficient and unique catalysis for the aldol reaction of aldehydes with ketene silyl acetals.[2] As an extension of these studies, we now wish to disclose the unique diastereocontrol in the Eu(III)-catalyzed cyanosilylation of chiral α-alkoxy- and α-aminoaldehydes with trimethylsilylcyanide (Scheme 1).



Scheme 1.

The reaction of an aldehyde with TMSCN (2.5 equiv.) was carried out in the presence of $Eu(fod)_3$ [3] (5 mol%) in CH_2Cl_2 at -40 °C for several hours. The crude product was desilylated with 1*N* HCl in THF. The stereochemical assignments were made on the basis of ^1H and ^{13}C NMR spectral comparison with authentic, stereo-defined samples prepared by the literature procedure,[4] and the diastereomeric ratios were determined by capillary GLC analysis. Table 1 summarizes the stereoisomer distributions thus obtained.

First, the Eu(III)-catalyzed cyanosilylation of α-benzyloxyaldehydes (**1**) was found to afford the syn adduct as the major product (entries 1, 3, 5), while a similar reaction of α-siloxyaldehydes (**2**) was non-

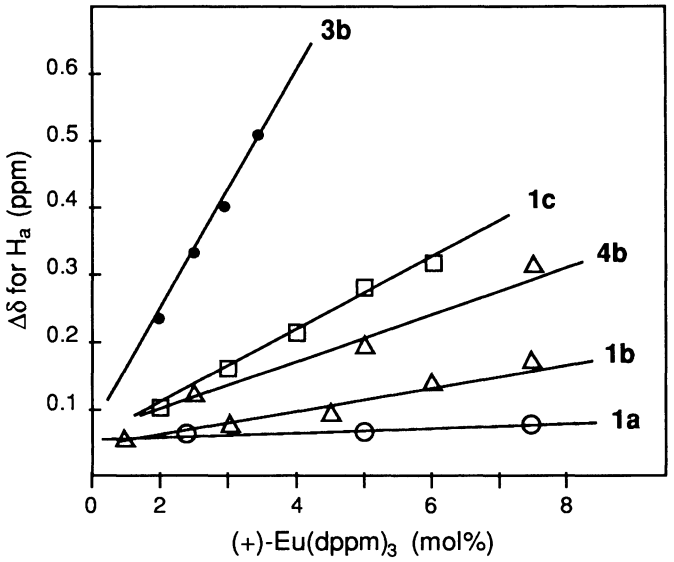
Table 1. $Eu(fod)_3$-catalyzed cyanosilylation

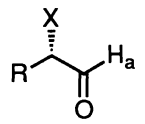
Entry	Aldehyde	Catalyst	syn	:	anti[a]	Yield/%[b]
1	X = OBn, R = Me (**1a**)	$Eu(fod)_3$	71	:	29	85
2[c]		$TiCl_4$ (1.0 equiv.)	77	:	23	76
3	X = OBn, R = *i*-Bu (**1b**)	$Eu(fod)_3$	84	:	16	98
4		$TiCl_4$ (1.0 equiv.)	69	:	31	58
5	X = OBn, R = *i*-Pr (**1c**)	$Eu(fod)_3$	88	:	12	62
6		$TiCl_4$ (1.0 equiv.)	63	:	37	50
7	X = $OSiMe_2Bu^t$, R = Me (**2a**)	$Eu(fod)_3$	50	:	50[d]	70
8	X = $OSiMe_2Bu^t$, R = *i*-Bu (**2a**)	$Eu(fod)_3$	45	:	55[d]	88
9	X = NBn_2, R = *i*-Bu (**3b**)	$Eu(fod)_3$	95	:	5	84
10[e]		$TiCl_4$ (1.0 equiv.)	88	:	12	63
11	X = NHBoc, R = *i*-Bu (**4b**)	$Eu(fod)_3$	76	:	24	82
12	X = NHBoc, R = $PhCH_2$ (**4d**)	$Eu(fod)_3$	82	:	18	80
13	X = NHBoc, R = *c*-$C_6H_{11}CH_2$ (**4e**)	$Eu(fod)_3$	84	:	16	87

a) Unless otherwise noted, the isomeric ratio was determined by capillary GLC (OV-1, 25 m) analysis. b) Refers to the combined yield after a short-column chromatography. c) Cited from Ref. 4a. d) The isomeric ratio was determined by ^{13}C NMR analysis and the stereochemistry has not been determined yet. e) Cited from Ref. 4b.

stereoselective (entries 7 and 8). Of special interest is that the syn-selectivity observed with **1** depends markedly on the steric bulkiness of the alkyl group (R) in aldehydes; the syn-selectivity increases from 71% to 88% on going from R=Me to R=*i*-Pr. Interestingly enough, this trend is opposite to what are observed in the $TiCl_4$ (1.0 equiv.)-promoted reactions (entries 2, 4, 6). Second, both the Eu(III)-catalyzed cyanosilylations of dibenzyl-protected (**3**) and *t*-butoxycarbonyl (Boc)-protected aminoaldehydes (**4**) also gave the syn adduct predominantly. Of special value is the remarkably enhanced syn selection observed with *N,N*-dibenzylleucinal compared with the *N*-Boc analogue (entry 9 *vs.* 10).[5]

In order to gain an insight to the mechanism of the present catalytic process, we carried out lanthanide induced shift (LIS)-NMR analysis of the aldehydes using $Eu(dppm)_3$ as the shift reagent.[6] Figure 1 shows the plots of the LIS magnitude ($\Delta\delta$) for the formyl-proton against the concentration of the shift reagent. In a series of α-benzyloxyaldehydes, the $\Delta\delta$-value at a given concentration of the shift reagent increases with increasing the bulkiness of the alkyl (R) group in aldehydes. This trend implys that the extent of chelation (bidentate) complexation by the Eu-complex to aldehydes decreases with increasing the bulkiness of R group. In other words, the mode of complexation for aldehyde **1c** (R=*i*-Pr) is almost non-chelation (monodentate), while **1a** (R=Me) forms preferentially the chelation (bidentate) complex.[7] Based on the same argument, the larger LIS magnitude observed with *N,N*-dibenzyl leucinal (**3b**) compared to the *N*-Boc analogue (**4b**) indicates that the chelation ability of the former is lower than that of the latter.





1a : X = OBn, R = Me

1b : X = OBn, R = *i*-Bu

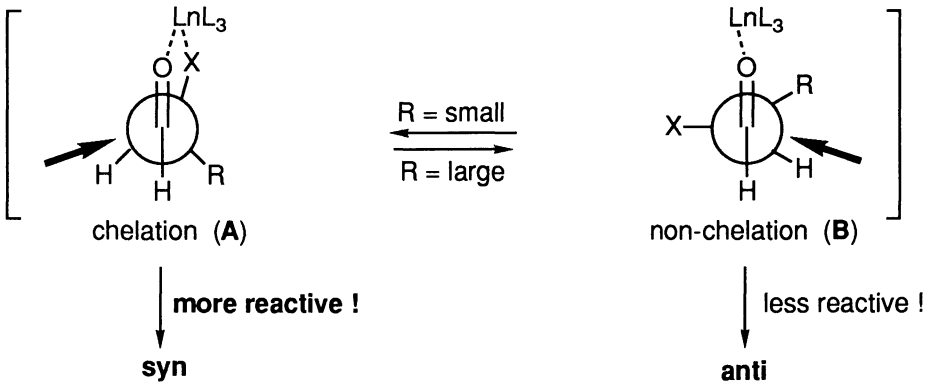
1c : X = OBn, R = *i*-Pr

3b : X = NBn_2, R = *i*-Bu

4b : X = NHBoc, R = *i*-Bu

Fig. 1. Lanthanide-induced shift (LIS)-NMR analysis.

In view of these arguments based on the LIS-NMR experiments, the stereochemical outcomes in the catalytic cyanosilylation described above are quite surprising because an aldehyde with *low* chelation ability such as **1c** and **3b** provides *high* syn selection.[8] Thus, we suggest that the Eu(III)-catalyzed cyanosilylation proceeds preferentially through the *more reactive* chelation complex(**A**)[9] to give selectively the chelation (syn) adduct, the degree increasing with an increase in the bulkiness of R group (Scheme 2).



Scheme 2.

In summary, this work has demonstrated that the Eu(III)-catalyzed cyanosilylation of chiral α-alkoxy and α-amino aldehydes, when the protective group is properly chosen, provides a relatively high level of syn (chelation) selection. The Eu(III)-catalyzed cyanosilylation of α-aminoaldehydes are potentially useful for the asymmetric synthesis of components of renin inhibitor such as norstatine.

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5) No adduct was obtained in a similar $Eu(fod)_3$-catalyzed reaction with *N, N*-dibenzylphenylalaninal.
6) $Eu(dppm)_3$ = tris[di(perfluoro-2-propoxypropionyl)methanate] europium(III). This shift reagent contains only three hydrogens and has a stronger shifting power than $Eu(fod)_3$, and hence provides more clear-cut information concerning the complexation.
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8) This is in sharp contrast to the Eu(III)-catalyzed aldol reaction with more reactive ketene silyl acetals, wherein a chelated aldehyde provides preferentially the chelation (syn) adduct, while a nonchelated aldehyde leads to the selective formation of the nonchelation (anti) product (Ref. 3).
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