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Stereo-Modulating Catalysis by Europium(III) Complexes in Aldol Reactions of Chiral α-Alkoxy Aldehydes with Ketene Silyl Acetals

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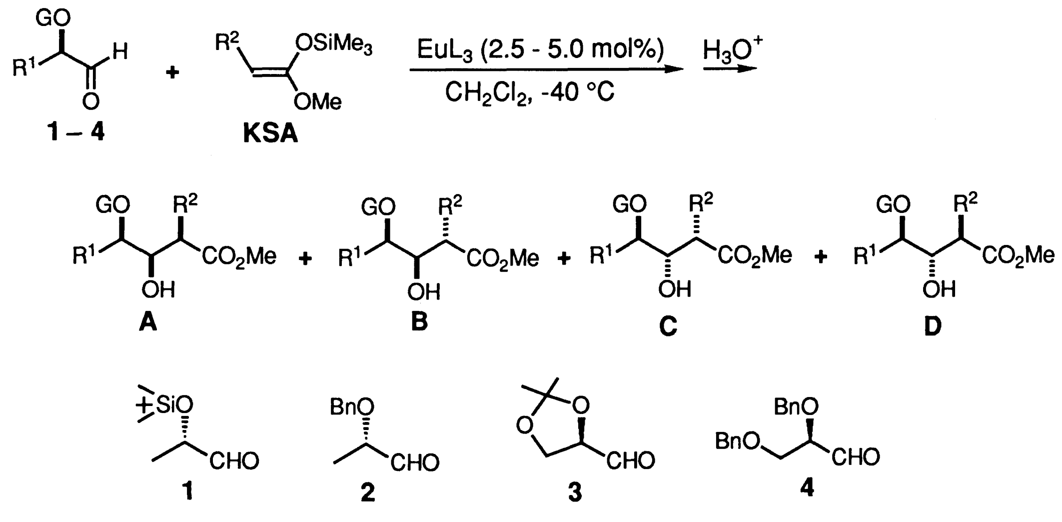
The Eu(fod)3- or Eu(dppm)3-catalyzed aldol reactions of the four chiral α-alkoxy aldehydes having different protecting groups with (*E*)- or (Z)-ketene silyl acetals are shown to provide the high levels of diastereocontrol, the sense depending on the nature of the protecting group. The catalytic stereo-modulation is explained in terms of the mode of aldehyde/catalyst complexation (chelation *vs*. nonchelation).

While much attention has recently been focused on enantioselective catalysis of aldol-type reactions,[1] the development of diastereoselective catalysis is synthetically valuable as well.[2] Of particular value but unexplored yet is the catalysis that allows not only for the selective formation of a specific stereoisomer but also for the effective modulation of the product stereochemistry. Disclosed herein is the "stereo-modulating" catalysis[3] by europium(III) complexes in the aldol reactions of chiral α-alkoxy aldehydes (**1-4**) with ketene silyl acetals (KSA) (Scheme 1).[4]



Scheme 1.

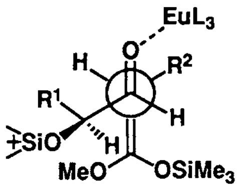
Table 1 summarizes the product distributions in the reactions of aldehydes **1-4** with (*E*)- or (Z)-KSA catalyzed by Eu(fod)3 or Eu(dppm)3[5] (NMR shift reagents). Inspection of the data reveals several significant features of the Eu(III)-catalysis. The most striking is that the stereochemistry of the major product not only varies critically with changing the protecting group in the aldehydes but also differs significantly from that observed for the conventional $TiCl_4$-promoted counterpart.[6] Thus, the remarkable levels of stereocontrol and stereo-modulation by the Eu(III)-catalysis are of both synthetic use and mechanistic interest.

Table 1. Eu(III)-Catalyzed Aldol Reactions[a]

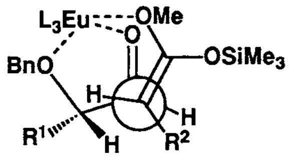
Entry	Aldehyde	R^2 in KSA	**A : B : C : D**[b]	Yield/%[c]
1[d]	**1**	Me (95%Z)	14 : 5 : 80 : 1	90
2[d]		Me (85%E)	3 : 2 : 94 : 1	80
3		OBn (100%Z)	5 : 2 : 93 : 0[e]	58
4	**2**	Me (95%Z)	34 : 66 : 0 : 0	79
5[d]		Me (95%Z)	23 : 73 : 4 : 0	95
6[d]		Me (85%E)	49 : 40 : 10 : 1	78
7		Et (95%Z)	8 : 92 : 0 : 0[e]	83
8		Et (90%E)	40 : 60 : 0 : 0[e]	76
9		OBn (100%Z)	2 : 98 : 0 : 0[f]	93
10		OMe (100%Z)	3 : 97 : 0 : 0	81
11		$OSiMe_3$ (85%Z)	2 : 98 : 0 : 0[g]	75
12[d]	**3**	Me (95%Z)	1 : 6 : 79 : 14[h]	85
13[d]		Me (85%E)	2 : 3 : 62 : 33[h]	82
14		OBn (100%Z)	18 : 33 : 49 : 0[i]	53
15	**4**	OBn (100%Z)	1 : 98 : 1 : 0[f]	87
16		OMe (100%Z)	3 : 95 : 2 : 0[f]	80

a) Unless otherwise noted, the reaction of aldehyde (1 equiv.) with KSA (1.2 equiv.) was carried out in the presence of $Eu(fod)_3$ (5 mol%) in CH_2Cl_2 at -40 °C for several hours. b) Unless otherwise noted, the isomeric ratio was determined by capillary GLC analysis and the product relative stereochemistry was determined by ^1H NMR analysis of their acetonides: *Cf.* S. Thaisrivong and D. Seebach, *J. Am. Chem. Soc.*, **105**, 7407 (1983) and Ref. 8a. c) Refers to the combined yield after a short-column chromatography. d) $Eu(dppm)_3$ (2.5 mol%) was used as the catalyst. e) The 2,3-relative stereochemistry of the major product was determined by ^1H NMR analysis of the β-lactam derivative obtained via the cyclization of the hydroxamate derived from the aldol: *Cf.* F. Shirai and T. Nakai, *Chem. Lett.*, **1989**, 445. f) The isomeric ratio was determined by HPLC analysis. g) The isomeric ratio was determined by GLC analysis of the acetonides. h) The product stereochemistry was determined by ^{13}C NMR analysis of the 1,3-diol obtained via $LiAlH_4$ reduction of the aldol: *Cf.* C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980). i) The isomeric ratio was determined by ^1H NMR analysis of the aldols but their stereochemistry has not been determined yet.

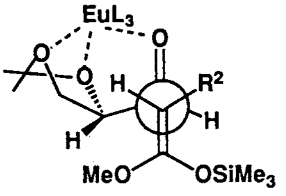
Aldehyde **1** affords selectively the product of type **C** (nonchelation/syn) via the widely recognized[6] antiperiplanar transition state (**X**). By contrast, both aldehydes **2** and **4** deliver preferentially the product of type **B** (α-chelation/ anti), the diastereoselectivity depending markedly on the KSA geometry (entries 5 *vs.* 6, 7 *vs.* 8). Of particular interest is the high anti diastereoselection observed with (*Z*)-KSA, in direct contrast to the high syn selection widely observed for the Mukaiyama reactions using a stoichiometric amount of $TiCl_4$.[6,7] The unusual stereochemical outcomes[8] are best rationalized by assuming the rarely precedented synperiplanar (or synclinal) transition state (**Y**)[9,10] that is favored by the additional binding of the chelated complex to the methoxy group of (*Z*)-KSA in particular. While aldehyde **4** coordinates with the catalyst only by the α-benzyloxy-oxygen,[6c] aldehyde **3** binds by both of the acetal-oxygens, thereby providing selectively the product of type **C** (α,β-chelation/syn),[11] again, through the antiperiplanar transition state (**Z**). Thus, the catalytic stereo-modulation is interpreted as a result of the variation in mode of the aldehyde/catalyst complexation which dictates the geometry of the aldol transition-state.



X ⟶ **C**



Y ⟶ **B**



Z ⟶ **C**

The ability of the aldehydes to bind with the Eu(III)-catalyst is likely to vary in the order: **1** (monodentate) < **2** (bidentate) < **3** (tridentate), as probed by the NMR shift experiments.[1g,12] Indeed, we found that the competitive reaction between **1** and **2** (1.0 equiv. each) with (Z)-KSA (R^2=Me, 1.0 equiv.) in the presence of $Eu(dppm)_3$ (2.5 mol%) gave the **2**-derived aldol in preference to the **1**-derived one in a ratio of 88 to 12. In a similar competition between **2** and **3**, the latter is the winner to provide preferentially the **3**-derived aldol in a ratio of 83 to 17.

In summary, this work convincingly demonstrates that the Eu(III)-catalyst can effectively discriminate the aldehyde structures, thereby providing the unique, stereo-modulating catalysis of the asymmetric aldol reactions concerned. Synthetic application of the interesting catalytic process and further extension of the stereo-modulating catalysis are in progress.

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4) We have recently disclosed the efficient catalysis by Eu(dppm)$_3$ of the aldol and Michael reactions with KSA: K. Mikami, M. Terada, and T. Nakai, *J. Org. Chem.*, **56**, 5456 (1991).

5) Eu(fod)$_3$ = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium(III). Eu(dppm)$_3$ = tris[di(perfluoro-2-propoxypropionyl)methanate] europium(III).

6) Reviews: a) T. Mukaiyama, *Org. React.*, **28**, 203 (1982); b) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); c) C. Gennari, "Selectivities in Lewis Acid Promoted Reactions," ed by D. Schinzer, Kluwer Academic Publ., Dordrecht (1989), Chap. 4.

7) In fact, we found that the TiCl$_4$-promoted reactions of **2** with (*Z*)-KSA gave only the chelation products (**A** and **B**), but the former syn-product predominating in a ratio of 86:14 for R^2=Me and 75:25 for R^2=Et. Note that similar TiCl$_4$-promoted reactions with (*E*)-KSA also yielded the product of type **A** preferentially, though the degree was slightly lower: *Cf.* M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron*, **40**, 4327 (1984).

8) It should be noted that the same chelation/anti selectivity as observed here is precedented. a) The aldol reaction of **2** with KSA(R^2=OBn) in the presence of 2 equiv. of Eu(fod)$_3$: K. Takai and C. H. Heathcock, *J. Org. Chem.*, **50**, 3247 (1985); b) The TiCl$_4$-promoted reaction of **2** with the (Z)-enol silyl ether of 3-pentanone: Reetz's unpublished results cited in his book: M. T. Reetz, "Organotitanium Reagents in Organic Synthesis," Springer-Verlag, Berlin (1986), p.135; c) The SnCl$_4$-promoted reaction of an α-stannylester with **2**: C. Gennari, M. G. Beretta, G. Moro, C. Scolastico, and R. Todeschini, *Tetrahedron*, **42**, 893 (1986); For the reaction of Ti-enolate with **2**, see: Ref. 7.

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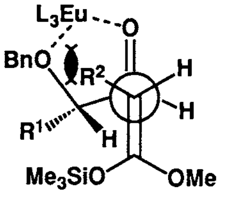
10) Alternatively, the unusual anti-diastereoselection might be explained by the antiperiplanar transition state (**Y'**) which, however, appears unlikely due to the large steric repulsion as indicated in the formula.



Y' ⟶ **B**

11) K. Mikami, M. Terada, and T. Nakai, *Tetrahedron Asymm.*, in press.

12) First, the LIS shift ($\Delta\delta_i$) for the β-hydrogens of each aldehyde was determined in a 0.05 M CDCl$_3$ solution containing 2.5 mol% of Eu(dppm)$_3$. Next, the LIS shift ($\Delta\delta_m$) for the β-hydrogens of each aldehyde was measured after the solutions of **1** and **2** or **2** and **3** were mixed. From these values, the catalyst was found to bind with **2** in preference to **1** in a ratio of 66:36 and with **3** in preference to **2** in a ratio of 55:36, as calculated by $[\Delta\delta_m / (\Delta\delta_i \times 2)] \times 100$.

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