Control of Chelation/Nonchelation Stereoselections in Lanthanide-catalysed Aldol Reactions

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A europium complex, [Eu(dppm)$_3$], can 'recognize' the difference in not only the protecting groups of α- or β-alkoxy aldehydes but also the size of ketene silyl acetals and catalyse either the chelation or nonchelation controlled-aldol reaction; {[Eu(dppm)$_3$] = tris[di(perfluoro-2-propoxypropionyl)methanato]europium(III)}.

The development of an efficient catalyst for C–C bond forming reactions is a subject of current intensive activity. Recently, chelation- and nonchelation-controlled aldol reactions have been developed as one of the most useful C–C bond forming reactions for acyclic stereocontrol.[1] However, the chelation and nonchelation selections have been attained by the strict choice of the Lewis acids (*e.g* $TiCl_4$, $SnCl_4$ *vs.* $BF_3{\cdot}OEt_2$) corresponding to the protecting groups of alkoxyaldehydes.[2] We report here that a unified europium catalyst, [Eu(dppm)$_3$] **1**,[3] can 'recognize' the difference in not only the protecting groups of aldehydes but also the size of the ketene silyl acetal (KSA) and hence dictate either chelation or nonchelation selections in the catalytic aldol reactions of α- and β-alkoxyaldehydes (**2–5**) with KSA **6** [eqn. (1)].[4,5]

Table 1 indicates the characteristic features of the [Eu(dppm)$_3$]-catalysed aldol reactions, wherein not only the degree but also the direction of 3,4-diastereofacial (chelation

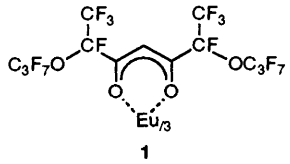

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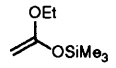
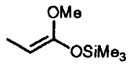
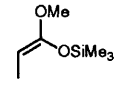
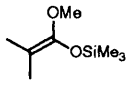
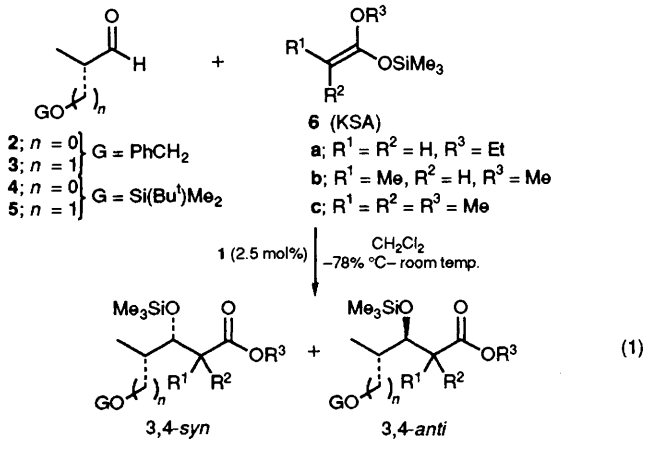
Table 1 [Eu(dppm)$_3$]-catalysed aldol reaction of alkoxyaldehydes with KSA[a]

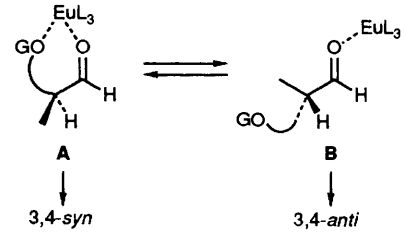
Entry	Aldehydes	KSA **6**	Conditions T/°C (t/h)	Yield (%)	Products 3,4-*syn* : 3,4-*anti*[b]
1	**2**	 **a**	−78 (3)	75	>99 : <1
			−40 (3)	72	>99 : <1 (98 : 2)[c]
2	**2**	 (*E*)-**b**[d]	−78 (3)	78	89[e] : 11 (>99 : <1)[c]
3	**2**	 (*Z*)-**b**[f]	−78 (3)	100	96[g] : 4
4	**2**	 **c**	−40 (6)	80	92 : 8
			0 (6)	92	84 : 16 (>99 : <1)[c]
5	**3**	**a**	−40 (6)	35	68 : 32
			0 (6)	90	62 : 38 (68 : 32)[c]
6	**3**	**c**	0 (6)	30	36 : 64 (>99 : <1)[c]
7	**4**	**a**	−40 (3)	90	74 : 26
8	**4**	(*E*)-**b**[d]	−40 (6)	80	5 : 95[h]
9	**4**	(*Z*)-**b**[f]	−40 (6)	90	19 : 81[i]
10	**4**	**c**	−40 (6)	55	29 : 71
			0 (6)	65	39 : 61
11	**5**	**a**	0 (3)	65	45 : 55
12	**5**	**c**	0 (6)	62	19 : 81

[a] All reactions were carried out using aldehyde (1.0 mmol), KSA (1.2 mmol) and **1** (0.025 mmol) in CH_2Cl_2 (3 ml). [b] Stereoisomeric ratio was determined by capillary GC analysis after desilylation of the products (ref. 5*c*). [c] $TiCl_4$ was used as an equimolar amount of promoter. [d] (*E*)-KSA (85%) was used. [e] 2,3-*syn* : *anti* = 49 : 40. [f] (*Z*)-KSA (95%) was used. [g] 2,3-*syn* : *anti* = 23 : 73. [h] 2,3-*syn* : *anti* = 94 : 1. [i] 2,3-*syn* : *anti* = 80 : 1.



(1)

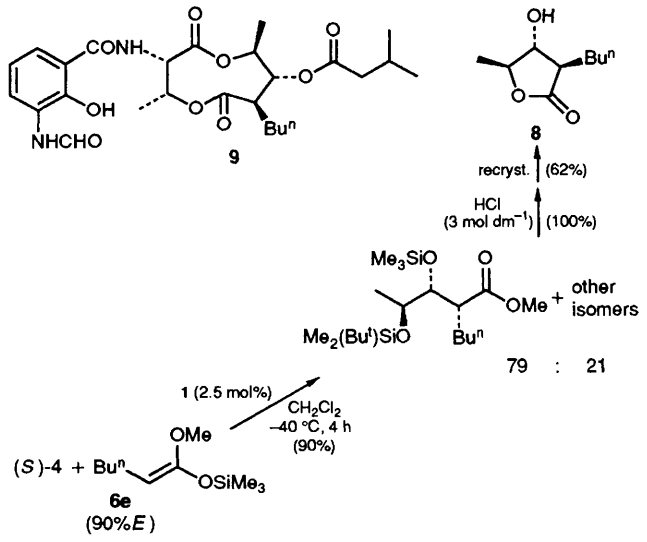
vs. nonchelation) selection are varied critically with the steric bulk of KSA **6**. The reaction of α-benzyloxyaldehyde **2** provides 3,4-*syn* (chelation) products (entries 1–4). Surprisingly, however, the degree of 3,4-*syn* selectivity decreases with increase in steric bulkiness of KSA. These observations are in sharp contrast to the general trend that 'the more bulky KSA are therefore the more selective',[1,2] as actually observed by a stoichiometric use of $TiCl_4$ (entries 1–6). Of particular interest is that the changeover in the sense of 3,4-selectivity from *syn* (chelation) to *anti* (nonchelation) is observed with the sterically bulky KSA **6c** in the reaction of β-benzyloxy



aldehyde **3** (entries 5 *vs.* 6). The *anti*-selectivity is in direct contrast to the high level of *syn*-selectivity observed for the $TiCl_4$-promoted counterpart[1,2] (entry 6). Furthermore, even in the reaction of α-siloxyaldehyde **4**, the least bulky KSA **6a** mainly provides the 3,4-*syn* product (74% selectivity), while the more bulky KSA **6b** exhibits the opposite 3,4-*anti* selectivity, the degree depending on the geometry of (*E*)- and (*Z*)-KSA (95 and 81% selectivities, respectively) (entries 7–10).

This control of the catalytic process is of interest not only from the synthetic but also the mechanistic viewpoint. In order to have an insight into the state of complexation (chelation **A** *vs.* nonchelation **B**) of [Eu(dppm)$_3$] and alkoxyaldehydes, we undertook LIS (lanthanide-induced shifts)-NMR analysis,[6] using 2-methylpropanal **7** as a reference (Table 2). The large K (S_b/S_a)† value of α-benzyloxyaldehyde **2** is evidence for the

† S_a: the slope of the observed LIS of the aldehydic protons. S_b: the slope of the observed LIS of the protons at α-position of aldehydes. Therefore, the proportion of $S_b/S_a(K)$ cancels out the association constant and influence of impurities.



Scheme 1

chelated complex **A**. In sharp contrast, the small K values of **7** and **5** indicate nonchelation complexation **B**. However, K values for β-benzyloxyaldehyde **3** and α-siloxyaldehyde **4** are somewhat larger than those observed for **7** and **5**, and hence imply averaged values in equilibrium between **A** and **B**, the latter complexation being favoured. Thus, in view of the Curtin–Hammett principle,[7] the diastereofacial selectivity in the [Eu(dppm)$_3$]-catalysed aldol reaction depends sensitively on the size of KSA; the sterically demanding KSA tends to react preferentially with the nonchelated complex **B** than with the congested chelation complex **A**.‡

Finally, we attempted to use this control of catalysis in the synthesis of blastomycinolactol **8** which is a degradation product of Antimycin A$_3$ **9**, an antifungal antibiotic (Scheme 1).[8] Thus, the appropriate stereoisomer (3,4-*anti*-2,3-*syn*), obtained by the combination of chiral aldehyde (*S*)-**4** with (*E*)-KSA **6e**, can be converted to corresponding lactones in quite short steps. The desired lactone **8** is purified by one recrystallization (hexane–Pr^{i}OH 4:1) in a highly scalable form: $[\alpha]_D$ −17.3 (*c* 1.29, MeOH), lit.[8a] $[\alpha]_D$ −18 (*c* 1.09, MeOH).

‡ As shown in Table 2, the chelation ability of these alkoxyaldehydes to [Eu(dppm)$_3$] is in the following order: α-benzyloxyaldehyde **2** ≫ β-benzyloxyaldehyde **3** > α-siloxyaldehyde **4** > 2-methylpropanal **7**, β-siloxyaldehyde **5**.

Table 2 Slopes (S_a and S_b) of the observed LIS *vs.* [Eu(dppm)$_3$]–aldehydes and the ratio of K (S_b/S_a)

Aldehyde	S_a[a,b] × 10^{-1}	S_b[a,c] × 10^{-1}	K (S_b/S_a)
2	0.04	1.74	43.5
3	1.40	1.24	0.89
4	2.46	1.82	0.74
5	2.34	1.54	0.66
7	2.06	1.38	0.67

[a] Values are derived from the best fit (linear regression) line for a set of data. Units are ppm × mol% of [Eu(dppm)$_3$]$^{-1}$. [b] S_a refers to the aldehydic protons. [c] S_b refers to the protons at α-position of aldehydes.

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