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Unique Stereocontrol in Lanthanide(III)-Catalyzed Aldol Reactions with the Ketene Silyl Acetal of Methyl (*R*)-3-Hydroxybutanoate

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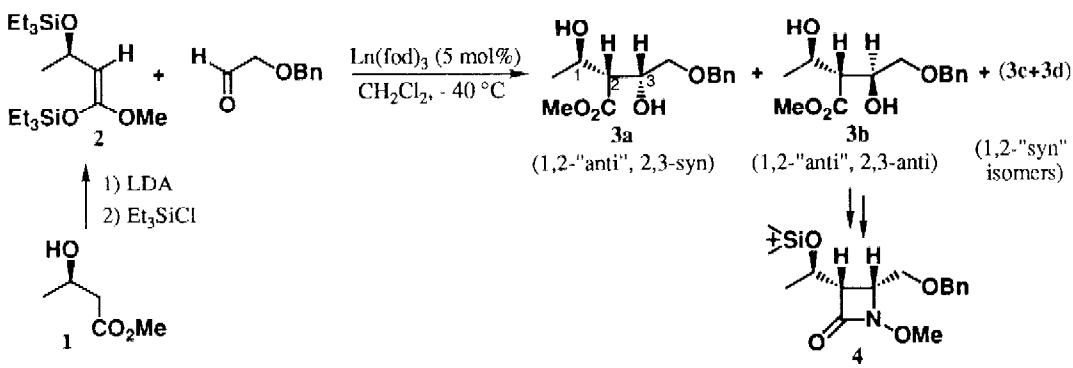
Abstract: The Eu(III)-catalyzed reaction of α-benzyloxyaldehydes with the (*R*)-3-hydroxybutanoate-derived ketene silyl acetal is shown to provide a higher level of both "anti" diastereofacial selection and rather unusual anti diastereoselection, compared with the conventional $TiCl_4$-promoted version. The aldol adducts are elaborated to the carbapenem intermediates.

Development of stereoselective catalysis of aldol-type reactions is the current subject of intense activities.[1,2] Recently we have reported that europium(III) complexes (NMR shift reagents) exhibit efficient and unique catalysis for the aldol reaction of aldehydes with ketene silyl acetals (KSA) in particular.[3,4] In a continuation of these studies, we became interested in the stereochemistry of the lanthanide-catalyzed aldol reaction with KSA of methyl (*R*)-3-hydroxybutanoate (**1**), a compound that has attracted much attention as a chiral building block, especially for carbapenem synthesis.[5] Our major concern here is how the sense and degree of the catalytic reaction are different from those of the conventional $TiCl_4$-promoted version.[6] Disclosed herein is that the $Eu(fod)_3$ and $Pr(fod)_3$ catalyzed reaction of benzyloxyacetaldehyde with the chiral KSA (**2**) provides a remarkably high level of rather unusual 2,3-anti diastereoselection together with a high 1,2-"anti" facial selection to afford selectively **3b** which is readily converted to the carbapenem intermediate **4** (Scheme 1).

Scheme 1



The reaction of the aldehyde with 1.2 equiv. of **2** (100% *Z*)[6] was carried out in the presence of $Ln(fod)_3$ (5 mol%) in CH_2Cl_2 at -40 °C for several hours. The crude products were desilylated with 1N HCl in THF. Table 1 summarizes the stereoisomer distributions thus observed. The stereochemical assignments were made on the basis of ^1H NMR analysis of their acetonide derivatives [6,7] and the stereoisomeric ratios were determined by capillary GLC analysis.

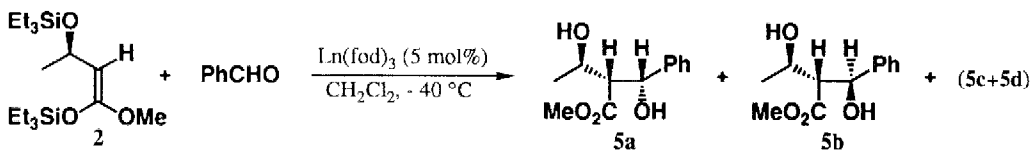
Table 1. Ln(fod)3 - Catalyzed Aldol Reactions of Benzyloxyacetaldehyde with (*R*)-**2**.

Entry	Catalyst	**3a** :	**3b** :	(**3c**+**3d**)[a]	Yield(%)[b]
1	$Pr(fod)_3$	1 :	97 :	2	71
2	$Eu(fod)_3$	0 :	96 :	4	62
3	$Ho(fod)_3$	19 :	81 :	0	82
4	$Yb(fod)_3$	23 :	67 :	10	78
5	$TiCl_4$ (1.0 equiv.)[c]	27 :	38 :	35	90

a) The ratios were determined by capillary GLC (Urbon HR 20M, 50 m). *b)* Refers to the combined yield after a short-column chromatography. *c)* The reaction was carried out at -78 °C.

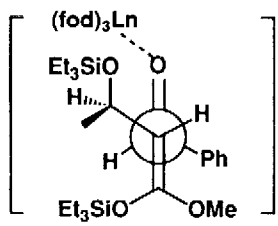
Inspection of the data in Table 1 reveals that the present catalytic reaction exhibits a much higher level of 1,2-"anti" facial selection along with a high level of rather unusual 2,3-anti diastereoselection, compared with the $TiCl_4$-promoted counterpart (entry 5). Of particular interest and value is the remarkably high 2,3-anti selectivity (entries 1 and 2) which contrasts with the high 2,3-syn selectivity observed in the similar catalytic reaction of benzaldehyde (Scheme 2). This difference is explicable in terms of the concept of chelation *vs.* non-chelation control as follows.

Scheme 2

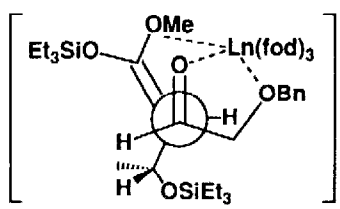


$Pr(fod)_3$	81 :	15 :	4	(58%)
$Eu(fod)_3$	95 :	3 :	2	(44%)
$TiCl_4$ (1.0 equiv.)	85 :	8 :	7	(75%)

While the 2,3-syn selectivity of the benzaldehyde reaction (non-chelation) is easily explained in terms of the widely recognized antiperiplanar transition state (**A**), the 2,3-anti selectivity of the benzyloxyacetaldehyde reaction (chelation) is best rationalized in terms of the rarely precedented synperiplanar transition state (**B**), analogous to the transition state previously proposed for the Eu-catalyzed reactions of a *chiral* α-benzyloxyaldehyde with *achiral* KSA's.[4]



A ⟶ 1,2-"anti", 2,3-syn

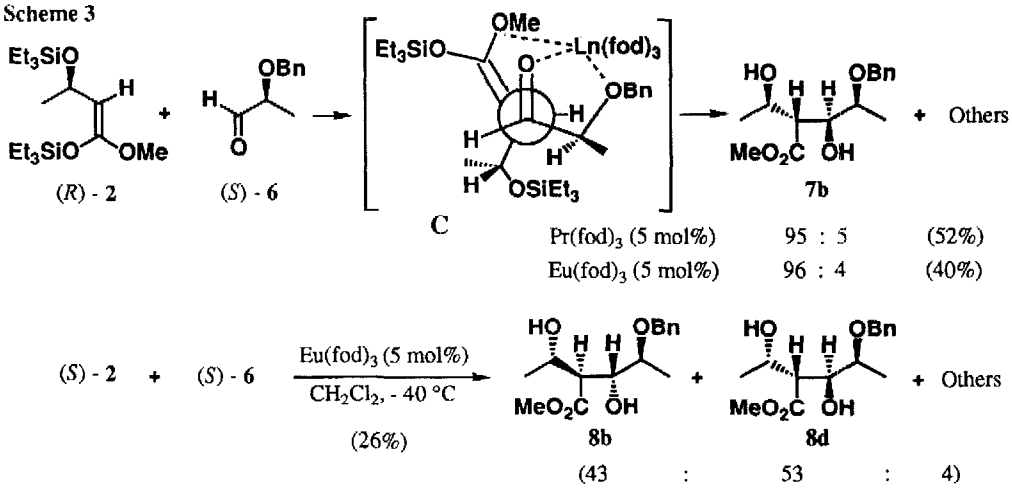


B ⟶ 1,2-"anti", 2,3-anti

To test this transition state model, we also carried out the double-asymmetric aldol reactions of (*R*)- or (*S*)-**2** with (*S*)-2-benzyloxypropanal (**6**) with the prediction that the (*R*)-**2**/(*S*)-**6** would be a matched pair in the present

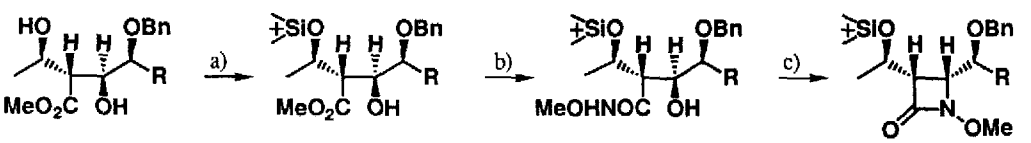
catalytic process, while (*S*)-**2**/(*S*)-**6** was a matched pair in the $TiCl_4$-promoted version.[6] Indeed, we found that the catalytic reaction of (*R*)-**2** with (*S*)-**6** afforded the aldol adduct **7b** (1,2-"anti", 2,3-anti) in a remarkably high selectivity, whereas the (*S*)-**2**/(*S*)-**6** pair provided an almost 1:1 mixture of the aldols **8b** and **8d** (Scheme 3).[8] The almost exclusive formation of **7b** is best understandable as a result of the favorable double stereodifferentiation in the synperiplanar transition state (C). Thus, it is likely that the chelation-controlled catalytic aldol reaction proceeds preferentially through the synperiplanar transition state in general.

Scheme 3



The transformation of aldols **3b** and **7b** to the corresponding β-lactam was carried out in the same manner as previously reported [9] (Scheme 4). Thus, **3b** was converted, after selective silylation, to the hydroxamate **11** which was then cyclized under the Mitsunobu condition to afford β-lactam **4**. Likewise, aldol **7b** was elaborated to β-lactam **13**. Both **4** and **13** are useful synthetic intermediates for carbapenem synthesis.[9]

Scheme 4



Reagents, conditions and yields: a) 2.0 equiv of t-$BuMe_2SiCl$, 2.5 equiv of imidazole, DMF, rt, 3 h; 65% for **3b**; 93% for **7b**; b) 6.0 equiv of $MeONH_2$ HCl, 6.0 equiv of Me_3Al, toluene, rt, 2 h; 88% for **9**; 82% for **10**; c) 3.0 equiv of Ph_3P, 3.0 equiv of $MeO_2CN{=}NCO_2Me$, THF, 0 °C, 1.5 h; 82% for **11**; 68% for **12**.

In summary, we have demonstrated that the $Eu(fod)_3$- or $Pr(fod)_3$-catalyzed aldol reaction of α-benzyloxyaldehydes with the chiral KSA (**2**) provides a high level of both diastereo- and diastereofacial selection through the rarely precedented synperiplanar transition state. Furthermore, the catalytic asymmetric aldol reaction is shown to provide a new and efficient method for the asymmetric synthesis of carbapenem intermediates. Further application of lanthanide catalysis is in progress.

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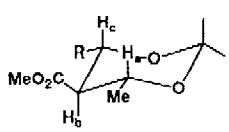
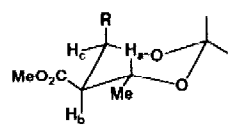
7. For similar stereochemical assignments of structurally related acetonides, see: Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407. The most informative are the coupling constants for the diastereomeric acetonides derived from the aldols **3a**, **5a** and **3b**, **5b** as exemplified below.



acetonide of **3a** and **5a**
$J_{ab} = J_{bc} = 10.2 \sim 10.5$ Hz



acetonide of **3b** and **5b**
$J_{ab} = 9.0 \sim 9.1$ Hz, $J_{bc} = 6.5 \sim 6.9$ Hz

8. The stereochemistry of aldols **7b**, **8b** and **8d** was assigned by the ^1H NMR analysis of their acetonides as described in Ref. 6. The J_{ab}- and J_{bc}-values thus observed are as follows, respectively: 8.8 and 5.9 Hz for **7b**; 9.0 and 5.4 Hz for **8b**; 3.0 and 3.0 Hz for **8d**.
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