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ESTER DERIVED TITANIUM ENOLATE ALDOL REACTION: HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF SYN- AND ANTI-ALDOLS

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Abstract: Aldol reactions of bidentate aldehydes and cis-1-arylsulfonamido-2-indanyl ester derived titanium enolates proceed with excellent syn-diastereoselectivities and good to excellent isolated yields. © 1997 Elsevier Science Ltd.

Asymmetric aldol reactions are often utilized in the synthesis of complex organic molecules of biological importance.[1] Over the years, numerous studies led to the development of a number of effective methodologies for syn[2] and anti-aldol[3] reactions. Recently, we reported[4] cis-1-arylsulfonamido-2-indanyl ester derived titanium enolate anti-aldol reactions with high diastereofacial selectivity. In our continuing effort to understand the origin of anti selectivity, we have now established that the choice of *p*-toluenesulfonamido group, the presence of indanyl ring and the choice of metal all are critical to observed anti-aldol diastereoselectivity. Furthermore, based on the possible transition state assembly, we speculated that the incorporation of a chelating substituent on the aldehyde side chain would alter the stereochemical outcome from an anti-aldol to a syn-aldol product. Herein, we report that indeed, the reactions of a number of ester derived titanium enolates with three representative bidentate oxyaldehydes proceeded with excellent syn diastereoselectivity (up to 99% de) with good to excellent isolated yields. The current methodology is convenient and has practical synthetic potential since either the syn or anti-aldol product can be prepared from the same chiral template in a stereopredictable fashion utilizing inexpensive and versatile titanium reagents.[5]

Enantiomerically pure 1S, 2R-sulfonamide **1**[4] was converted to propionate ester **2a** with propionyl chloride and pyridine in CH_2Cl_2 at 0°C for 1 h (84% yield). The acylation of **1** with hydrocinnamic acid and 4-methylvaleric acid with DCC and DMAP afforded the respective esters **2b** and **2c** in 85% and 74% yield. Various titanium enolates of **2a-c** were generated by reaction of the respective ester with $TiCl_4$ (1.2 equiv) in CH_2Cl_2 at 0-23°C for 15 min followed by addition of N-ethyldiisopropylamine (4 equiv) at 23°C and stirring of the resulting brown solution for 2 h. The titanium enolate was then added to the representative aldehyde (2 equiv) precomplexed with $TiCl_4$ (2.2 equiv) at -78°C and the mixture was stirred at -78°C for 2 h before quenching with aqueous NH_4Cl. As shown in Table I, aldol reactions of **2a-c** derived titanium enolates with various homologous oxyaldehydes proceeded with excellent syn-diastereoselectivity whereas reactions with a representative aliphatic aldehyde such as isovaleraldehyde, proceeded with excellent anti-

diastereoselectivity. The syn-anti mixture ratio was determined by ^{1}H NMR (400 MHz) as well as by reverse phase HPLC before and after chromatography. Aldol reactions of benzyloxyacetaldehyde[6]

Table 1. Aldol reaction of various esters **2a-c** with representative aldehydes

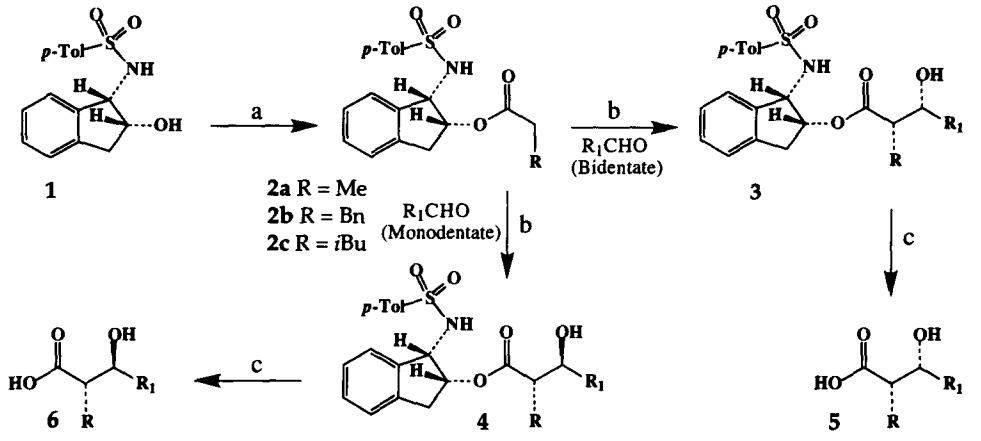
Entry	Ester	Aldehyde	Compd[a]	% Yield[b]	Syn:Anti (**3/4**)[c]
1.	**2a**	$BnOCH_2CHO$	**3a**	84	98 : 2
2.	**2a**	$BnO(CH_2)_2CHO$	**3b**	51	98 : 2
3.	**2b**	$BnOCH_2CHO$	**3c**	84	99 : 1
4.	**2b**	$BnO(CH_2)_2CHO$	**3d**	51	99 : 1
5.	**2b**	$BnO(CH_2)_3CHO$	**3e**	55	94 : 6
6.	**2c**	$BnOCH_2CHO$	**3f**	83	99 : 1
7.	**2c**	$BnO(CH_2)_2CHO$	**3g**	56	99 : 1
8.	**2a**	*i*BuCHO	**4i**	92	1 : 99
9.	**2b**	*i*BuCHO	**4j**	91	1 : 99
10.	**2c**	*i*BuCHO	**4k**	83	1 : 99

[a]Only isolated product; **3a** (R=Me, R_1=CH_2OBn); **3b** (R=Me, R_1=$(CH_2)_2OBn$); **3c** (R=Bn, R_1=CH_2OBn); **3d** (R=Bn, R_1=$(CH_2)_2OBn$); **3e** (R=Bn, R_1=$(CH_2)_3OBn$); **3f** (R=*i*Bu, R_1=CH_2OBn); **3g** (R=*i*Bu, R_1=$(CH_2)_2OBn$); **4i** (R=Me, R_1=*i*Bu); **4j** (R=Bn, R_1=*i*Bu); **4k** (R=*i*Bu, R_1=*i*Bu); [b] Isoiated yield after chromatography. [c] Ratios determined by ^{1}H-NMR and HPLC analysis before and after chromatography. Reaction time = 1.5-2 h.

with propionate derivative **2a**, hydrocinnamate derivative **2b** and 4-methylvalerate derivative **2c** have afforded virtually a single syn-isomer in excellent isolated yield. Similarly, reactions of these esters with benzyloxypropionaldehyde provided excellent syn-diastereoselectivity, but with relatively lower isolated yields. The aldol reaction of **2b** with benzyloxybutyraldehyde[6] also afforded a syn-aldol product with slightly lower selectivity compared to other oxyaldehydes. In contrast, reactions of isovaleraldehyde with **2b** and **2c** have resulted in anti-aldol reaction with excellent anti-diastereoselectivity and isolated yields.

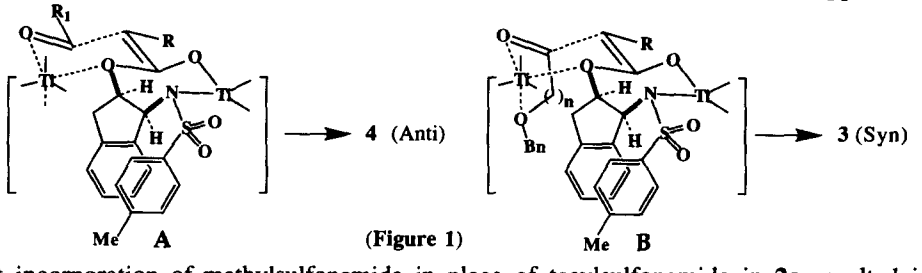
The assignment of relative and absolute stereochemistry of various syn aldolates **3** (entry 1 to 7) was firmly established after removal of the chiral template. The comparison of ^{1}H-NMR and ^{13}C-NMR spectra as well as the optical rotation of the resulting acids **5** were compared against the authentic optically pure samples prepared utilizing the boron enolate[2a] aldol reaction.[7] The removal of the chiral template was effected by exposure to lithium hydroperoxide in THF at 23°C for 2-3 h affording the corresponding β-hydroxy acid in 84-95% yield. The chiral template **1** was fully recovered without loss of optical purity (α_D^{23} +34.2, c 1.8, $CHCl_3$). Alternatively, the hydrolysis of aldol adduct can be carried out with aqueous lithium hydroxide in THF at 23°C. However, a much longer reaction time is required for complete hydrolysis (for **3**, 18-24 h).

To rationalize the anti-aldol stereoselectivities with monodentate aldehydes, we previously[4] postulated a Zimmerman-Traxler[8] type transition state model **A** in which the metalocycle is assumed to



Scheme I : (a) CH_3CH_2COCl, pyridine, CH_2Cl_2, 0°C, 1 h for **2a**; RCO_2H, DCC, DMAP, CH_2Cl_2, 23°C, 18-24 h for **2b-c** ; (b) $TiCl_4$, iPr_2NEt, 23°C then R_1CHO and $TiCl_4$, CH_2Cl_2, -78°C, 2 h; (c) LiOH, 30% H_2O_2, THF-H_2O, 23°C, 2-3 h.

adopt a chair-like conformation with a possible π-stacking interaction between the aromatic rings. This model is the basis of our further speculation that the addition of a chelating substituent on the aldehyde side chain would result in a transition state assembly such as **B**.[9] The observed syn-stereoselectivity of bidentate aldehydes is consistent with this postulated model. The present syn-stereoselectivity can also be explained by an acyclic transition state similar to that proposed by Gennari *et al.*[10] The enhanced selectivity for benzyloxyacetaldehyde and benzyloxy-propionaldehyde compared to benzyloxybutyraldehyde is most likely due to effective metal chelation through five and six membered transition states rather than a less favorable seven membered ring system. The involvement of crucial metal chelation was further evidenced by the fact that the reaction of enolate of **2a** with *tert*-butyldiphenylsilyloxyacetaldehyde afforded a 70:30 mixture of syn/anti aldol products due to steric bulk of the surrounding ether oxygen which hinders effective chelation. The possible aromatic π-stacking interaction in the transition state model is supported by



(Figure 1)

the fact that incorporation of methylsulfonamide in place of tosylsulfonamide in **2a** resulted in a mixture (70:30) of anti/syn diastereomers with isovaleraldehyde (through **B**). Furthermore, removal of the indane aromatic ring in **2a** also resulted in a mixture (50:50) of syn/anti diastereomers.[11] Further evidence for such a π–stacking interaction is the subject of ongoing investigation.

In summary, an ester derived titanium enolate based highly selective (96-98% de) syn-aldol process has been developed. The reaction of the same titanium enolate with monodentate aldehyde however provides anti-aldol product with excellent diastereoselectivity. Thus, with proper choice of chiral template and aldehyde one can prepare either syn- or anti-aldol product in a stereopredictable fashion. Synthetic applications and mechanistic investigations are currently in progress.

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