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Chelation-controlled ester-derived titanium enolate aldol reaction: diastereoselective *syn*-aldols with mono- and bidentate aldehydes

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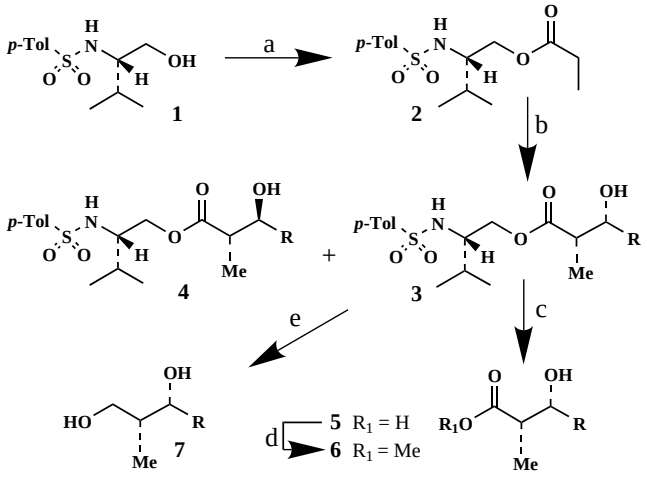
Abstract—A chelation-controlled and highly diastereoselective synthesis of *syn*-aldols is described. Aldol reaction of (*S*)-valinol-derived ester with a variety of aldehydes proceeded with high *syn*-diastereoselectivities (up to 99:1) and isolated yields (94%).

Optically active *syn*- and *anti*-2-alkyl-3-hydroxycarbonyl units are inherent to numerous biologically active natural products.[1] As a consequence, a number of stereoselective methodologies have been developed for their syntheses.[2,3] In our recent work on ester-derived titanium enolate aldol reactions[4] we have demonstrated that the aldol reactions of phenylalaninol-derived sulfonamido esters with a number of bidentate oxyaldehydes provided *syn*-aldols diastereoselectively. The corresponding reactions with monodentate aldehydes, however, have shown little *syn*-selectivities. The chirality transfer presumably proceeds through chelation by the β-sulfonamide functionality. In our continuing effort to further develop these ester-derived titanium enolate aldol reactions, we have subsequently investigated the effect of a β-chiral substituent on aldol stereochemistry by replacing the phenylmethyl substituent of phenylalaninol with other alkyl groups. Herein, we report that the aldol reaction of an (*S*)-valinol-derived sulfonamido ester with a variety of mono- and bidentate aldehydes proceeded with good to excellent *syn*-diastereoselectivities and isolated yields. Removal of the chiral auxiliary by mild saponification provided optically active *syn*-α-alkyl-β-hydroxy acids and full recovery of the chiral auxiliary. The ready availability of valinol and use of inexpensive $TiCl_4$ make this methodology practical and provide rapid access to *syn*-aldols in optically active form.

Optically active *N*-*p*-tosyl-(2*S*)-valinol **1** was prepared in multigram quantities by reduction of L-valine with $LiAlH_4$ and followed by sulfonylation of the amine functionality with *p*-toluenesulfonyl chloride and triethylamine in the presence of DMAP at 0°C for 2 h (89% yield). As shown in Scheme 1, reaction of sulfonamide **1** with propionylchloride and triethylamine afforded propionyl ester **2** in 85% yield after silica gel chromatography (mp 78°C, $[\alpha]_D^{23} = -19.1$ (*c* 0.92, $CHCl_3$)). The corresponding titanium enolate of **2** was prepared by treatment with $TiCl_4$ (1.1 equiv., 1 M solution in CH_2Cl_2) in CH_2Cl_2 at 0°C followed by addition of *N*,*N*′-diisopropylethylamine (3 equiv.) after 10 min and stirring of the resulting mixture at 0°C for 1 h. The enolate so formed was reacted with a variety of aldehydes precomplexed with $TiCl_4$ (3 equiv.) at



Scheme 1. *Reagents and conditions*: (a) CH_3CH_2COCl, Et_3N, CH_2Cl_2, 0°C, 2 h; (b) $TiCl_4$, *i*Pr_2NEt, 0°C, 1 h, then RCHO and $TiCl_4$, CH_2Cl_2, −78°C, 2 h; (c) LiOH, THF–H_2O, 23°C, 2–3 h; (d) CH_2N_2, Et_2O, 23°C, 30 min; (e) $LiBH_4$, THF–MeOH, 23°C, 2 h.

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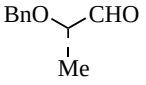
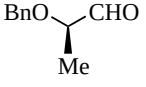
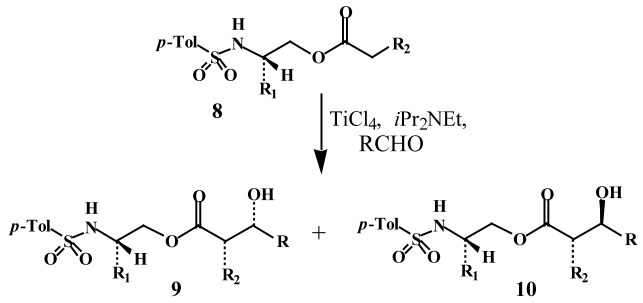
−78°C for 1.5–2 h. Interestingly, aldol reaction of **2** with various aldehydes proceeded with excellent diastereoselectivity and isolated yields; the results are summarized in Table 1. Out of four possible diastereomers, formation of *syn*-diastereomer **3** (major) and *anti*-diastereomer **4** were observed by ^{1}H and ^{13}C NMR as well as HPLC analysis before and after chromatography. Reaction of **2** with monodentate aldehydes exhibited high *syn*-diastereoselectivity (entries 1–5)[8] except with phenylpropargyl aldehyde which afforded the *anti*-isomer as the major product (entry 6). Furthermore, reaction with bidentate aldehydes such as benzyloxyacetaldehyde and benzyloxypropionaldehyde provided a single *syn*-aldolate in high yield (entries 7 and 8). We have also carried out double stereodifferentiating experiments in which an oxyaldehyde bearing an α-chiral center was reacted with the chiral enolate derived from propionate ester **2**. Aldol reaction of **2** and 2(*S*)-benzyloxypropionaldehyde (stereochemically matched case) under identical conditions afforded virtually a single (by HPLC and 400 MHz ^{1}H NMR analysis) aldol product **3h** (entry 9) in 77% yield after silica gel chromatography. However, the reaction of **2** and

Table 1. Aldol reaction of ester **2** with representative aldehydes

Entry	Aldehyde	Compd[a]	Yield (%)[b]	*syn*:*anti* (**3**/**4**)[c]
1	Me_2CHCHO	**3a**	89	90:10
2	Me_2CHCH_2CHO	**3b**	93	95:5
3	*trans*-PhCH=CHCHO	**3c**	89	96:4
4	PhCHO	**3d**	94	88:12
5	$Me(CH_2)_6CHO$	**3e**	96	82:18
6	Ph-C≡C-CHO	**3f**	86	36:64[d]
7	$BnOCH_2CHO$	**3g**	74	99:1
8	$BnOCH_2CH_2CHO$	**3h**	81	99:1
9		**3i**	77	99:1
10		**3j**	82	34:66[d]

[a] Major isolated product.
[b] Isolated yield after chromatography.
[c] Ratios determined by ^{1}H MR and HPLC analysis before and after chromatography. Reaction time = 1.5–2 h.
[d] Ratio after removal of chiral auxiliary.



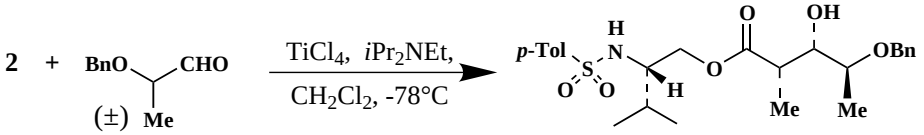
Scheme 3.

2(*R*)-benzyloxypropionaldehyde, a mismatched case, afforded a 34:64 mixture of *syn* and *anti* isomers in 82% isolated yield (entry 10). Because of the marked stereochemical preference (matched isomer), we then attempted reaction of **2** (1 equiv.) with racemic benzyloxypropionaldehyde (2 equiv.) at −78°C for 0.5 h (Scheme 2).

Interestingly, **2**-derived Ti-enolate reacted exclusively with the 2(*S*)-benzyloxypropionaldehyde (1 equiv.) under these reaction conditions providing only diastereomer **3i** (matched case) in 82% isolated yield after silica gel chromatography. Separation and purification of the corresponding unreacted enantioenriched 2(*R*)-benzyloxypropionaldehyde was difficult due to overlapping by-product. Subsequently, the crude aldehyde was reduced with $NaBH_4$ in ethanol at 23°C to afford 2(*R*)-(benzyloxy)propanol with an enantiomeric excess of 81% ee (41% recovered, $[\alpha]_D^{23} = -36.2$ (*c* 1.9, $CHCl_3$); lit.:[9] $[\alpha]_D^{20} = -45$ (*c* 1.0, $CHCl_3$).

The relative and absolute stereochemistry of various *syn*-aldolates (**3**) were established based upon comparison of optical rotation as well as ^{1}H and ^{13}C NMR spectra of the resulting acids, esters or diols with literature values.[5] Thus, saponification of the above aldolates with aqueous lithium hydroxide in THF at 23°C for 2 h furnished the corresponding β-hydroxy acids (**5**). Treatment of these acids with CH_2N_2 afforded the corresponding methyl esters (**6**). Various aldolates were converted to diols **7** by treatment with $LiBH_4$ at 23°C for 2–4 h. In either case, the chiral auxiliary was fully recovered without loss of optical activity.

We subsequently investigated substituent effects on the chiral auxiliary as well as the influence of various achiral and chiral bases on diastereoselectivity. As shown in Scheme 3, we have examined ester enolate aldol reactions of *N*-*p*-tosyl-(*S*)-*tert*-leucinol and *N*-*p*-



3i (82% yield, 99:1 *dr)*

Scheme 2.

Table 2. Aldol reaction of various esters with representative aldehydes

Entry	Ester	Aldehyde	Base (equiv.)	Yield (%)[a]	*syn*:*anti* (**9**/**10**)[b]
1	$R_1 = t$Bu, R_2 = Me	Me_2CHCHO	DIPEA (3)	35	90:10
2	$R_1 = i$Bu, R_2 = Me	Me_2CHCHO	DIPEA (2.5)	73	85:15
3	R_1 = Bn, R_2 = Me	Me_2CHCHO	DIPEA (2.5)	86	86:14
4	$R_1 = i$Bu, R_2 = Me	Me_2CHCHO	(−)-Spartein (2.2)	63	88:12
5	$R_1 = i$Bu, R_2 = Me	Me_2CHCHO	Et_3N (2.5)	83	88:12
6	$R_1 = i$Bu, R_2 = Me	PhCHO	Et_3N (2.5)	77	85:15
7	$R_1 = i$Bu, R_2 = Me	Ph-C≡C-CHO	Et_3N (2.5)	83	14:86
8	$R_1 = i$Bu, R_2 = Me	$BnOCH_2CHO$	DIPEA (3)	80	99:1
9	$R_1 = i$Pr, $R_2 = i$Bu	$Me_2(CH_2)_2CHO$	DIPEA (3)	97	87:13

[a] Isolated yield after chromatography.
[b] Ratios determined by ^{1}H NMR before and after chromatography.

tosyl-(*S*)-leucinol-derived esters and a number of aldehydes. The results of these various aldol reactions are illustrated in Table 2. As can be seen, the sterically demanding *tert*-leucinol-derived chiral auxiliary exhibited lower yield over leucinol-derived auxiliary; however, stereoselectivities were comparable (entries 1 and 2). The phenylalaninol-derived chiral auxiliary has also shown comparable *syn*-diastereoselectivity under the reaction conditions described above (entry 3). Interestingly however, the same aldol reaction with fewer equivalents of $TiCl_4$ precomplexed to isovaleraldehyde displayed *anti*-diastereoselectivity.[10] Such reversal in diastereoselectivity is not totally unexpected as the Lewis acid to aldehyde ratio is known to effect aldol stereoselectivity.[11] The choice of base is quite important for reaction yield but does not seem to effect observed stereoselectivity (entries 3–5). The chirality on the base has little influence on diastereoselectivities. Bidentate oxyaldehydes are in general very good substrates for ester enolate aldol reactions, providing *syn*-aldolates in excellent yields and diastereoselectivities (entry 8). The valinol-derived chiral auxiliary has also shown very good *syn*-diastereoselectivity and reaction yield with isocaproate ester (entry 9).

In summary, we devised a chelation-controlled ester-derived titanium enolate-based highly diastereoselective *syn*-aldol reaction with various aldehydes. The current methodology is quite practical due to the ready availability of optically pure chiral auxiliary and use of inexpensive $TiCl_4$ as the key reagent. Further mechanistic investigations, effects of various sulfonamido functionalities and synthetic applications are underway in our laboratories.

Acknowledgements

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5. Optical rotation of corresponding carboxylic acids, diols and methylesters ($CHCl_3$ solvent for all, unless otherwise noted), **5g**: $[\alpha]_D^{23}=+13.6$ (*c* 1.1), lit.:[4c] $[\alpha]_D^{23}=+12.97$ (*c* 3.7); **7a**: $[\alpha]_D^{23}=-10.29$ (*c* 0.68), lit.:[6] $[\alpha]_D^{25}=-10.3$ (*c* 0.2); **7c**: $[\alpha]_D^{23}=+12.2$ (*c* 0.83, MeOH), lit.:[7] $[\alpha]_D^{25}=+15.1$ (*c* 0.55, MeOH); **6b**: $[\alpha]_D^{23}=+16$ (*c* 0.48), sample prepared from Evans aldol: $[\alpha]_D^{23}=+12$ (*c* 0.13).
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8. All new compounds gave satisfactory spectroscopic and analytical results. Preparation of *syn*-aldol **3b**: To a stirred solution of propionate ester **2** (313 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0°C was added a 1 M solution of $TiCl_4$ (1.1 mL, 1.1 mmol) dropwise under a N_2 atmosphere. The resulting solution was stirred for 10 min. To this solution was added *N*,*N*-diisopropylethylamine (0.52 mL, 3 mmol) in a dropwise manner. The mixture was stirred for 1 h at 0°C and then warmed to 23°C. In a separate flask, to a stirred solution of isovaleraldehyde (172 mg, 2 mmol) in CH_2Cl_2 (20 mL) at −78°C under N_2 atmosphere, was added a 1 M solution of $TiCl_4$ (3 mL, 3 mmol). After stirring for 10 min, the above enolate solution was added to this aldehyde solution dropwise via cannula over 30 min. The mixture was stirred at −78°C for 1.5 h before quenching by aqueous NH_4Cl. The resulting mixture was warmed to 23°C and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the aldol products. Silica gel chromatography of the crude product yielded the aldol product (363 mg, 93%) as a viscous oil. Compound **3b**: $[\alpha]_D^{23}=-19.6$ (*c* 1.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, 6H, $J=6.9$ Hz), 0.84 (d, 6H, $J=6.9$ Hz), 1.10 (d, 3H, 7.1 Hz), 1.43 (m, 1H), 1.77 (m, 2H), 2.38 (m, 2H), 2.41 (s, 3H), 2.48 (br, 1H), 3.34 (m, 1H), 3.95 (dd, 1H, $J=11.6$, 4.5 Hz), 4.01 (m, 1H), 4.06 (dd, 1H, $J=11.6$, 5.9 Hz), 5.17 (d, 1H, $J=9.0$ Hz), 7.28 (d, 2H, $J=8.3$ Hz), 7.75 (d, 2H, $J=8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 18.3, 18.9, 21.5, 21.9, 23.4, 24.6, 30.0, 42.9, 44.7, 57.9, 64.0, 69.6, 127.0, 129.6, 138.2, 143.3, 175.8; IR (neat): 3521, 3286, 1730, 1327, 1161 cm^{-1}.
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10. Reaction of titanium enolate of **8** ($R_1=Bn$, $R_2=Me$) with isovaleraldehyde (2 equiv.) precomplexed with 1.05 equiv. of $TiCl_4$ at −78°C afforded a mixture of *anti* and *syn* diastereomers (70% yield). Removal of chiral auxiliary provided *anti*/*syn* ratio of 68:32. We have previously reported a 70:30 *anti*/*syn* ratio and 70% yield for this reaction. See: Ref. 4a.
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