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# Ester derived titanium enolate aldol reaction: chelation controlled diastereoselective synthesis of *syn*-aldols

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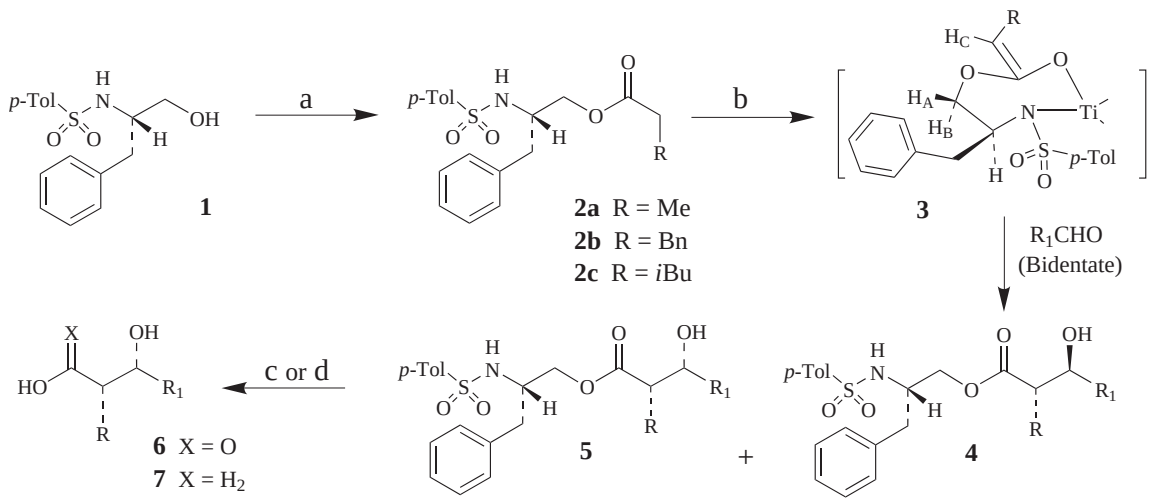
**Abstract**—A chelation controlled and highly diastereoselective synthesis of *syn*-aldols is described. Aldol reaction of commercially available L-phenylalaninol derived esters with a variety of bidentate oxyaldehydes proceeded with excellent *syn*-diastereoselectivities and isolated yields. © 2001 Elsevier Science Ltd. All rights reserved.

The asymmetric aldol reaction is one of the most powerful carbon–carbon bond forming reactions in organic synthesis.[1] Both *syn*- and *anti*-aldols are often inherent to numerous biologically active natural products and a number of stereoselective methodologies have been developed for their effective synthesis.[2,3] We recently reported a *cis*-1-arylsulfonamido-2-indanyl ester derived titanium enolate based novel stereoselective *anti*-aldol reaction.[4a] Subsequently, utilizing the same chiral auxiliary, we developed an efficient *syn*-aldol reaction with bidentate oxyaldehydes.[4b] Based upon our proposed chelated transition-state assembly, we speculated that the presence of an indane ring or the presence of an α-chiral center may not be critical to high observed *syn*-diastereoselectivities with the bidentate oxyaldehydes. To further understand the origin of *syn*-selectivities, we have now investigated aldol reactions of phenylalaninol derived sulfonamido esters with a view to generating *syn*-aldols diastereoselectively by a chelation through the β-sulfonamide functionality. To extend the utility of these aldol processes, we herein report that the reaction of sulfonamido ester derived titanium enolates with a number of bidentate oxyaldehydes provided *syn*-aldol products with excellent diastereoselectivities (up to 99% de) and isolated yields. Mild saponification resulted in various optically active




**Scheme 1.** (a) $CH_3CH_2COCl$, $Et_3N$, $CH_2Cl_2$, 0°C, 1 h for **2a**; $RCO_2H$, DCC, DMAP, $CH_2Cl_2$, 23°C, 18–24 h for **2b** and **2c**; (b) $TiCl_4$, $iPr_2NEt$, 0°C, 1 h then $R_1CHO$ and $TiCl_4$, $CH_2Cl_2$, −78°C, 2 h; (c) LiOH, THF–$H_2O$, 23°C, 2–3 h; (d) $LiBH_4$, THF, 23°C.

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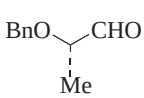
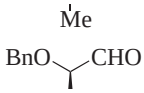
*syn*-α-alkyl-β-hydroxy acids and full recovery of the chiral auxiliary without loss of optical purity. The ready availability of both enantiomers of phenylalaninol, as well as the use of inexpensive titanium tetrachloride reagent make the present *syn*-aldol process particularly useful.

As depicted in Scheme 1, commercially available and optically active (2*S*)-phenylalaninol was reacted with *p*-toluenesulfonylchloride and triethylamine in $CH_2Cl_2$ in the presence of a catalytic amount of DMAP to provide optically pure (2*S*)-sulfonamide **1** in 95% isolated yield ($[\alpha]_D^{23} = -29.4$, *c* 2.5, $CHCl_3$). Reaction of sulfonamide **1** with propionyl chloride and triethylamine in $CH_2Cl_2$ at 0°C for 1 h afforded the propionate ester **2a** in 93% yield after silica gel chromatography. Acylation of **1** with hydrocinnamic acid and 4-methylvaleric acid with DCC and DMAP afforded the respective esters **2b** and **2c** in 86 and 87% yield. The corresponding titanium enolates of these esters were generated by slightly modified conditions. For example, propionyl ester **2a** was reacted with 1 M $TiCl_4$ (1.05 equiv.) in $CH_2Cl_2$ at 0°C and after 15 min, *N*,*N*-diisopropylethylamine (3 equiv.) was added and the resulting mixture was stirred at 0°C for 1 h. Complete enolization under these conditions was established by $^1H$ NMR (500 MHz) studies of the titanium enolate generated in a mixture of $CDCl_3$ and $CH_2Cl_2$. We speculated that the enolization proceeds through formation of a N–Ti bond followed by intramolecular Lewis acid activation of the ester carbonyl. The enolate is a seven-membered metallocycle **3**, presumably with a *Z*-enolate geometry.[5] The enolate so formed was reacted with various oxyaldehydes precomplexed with $TiCl_4$ (2.1 equiv.) at −78°C for 2 h to provide the respective aldol products in good to excellent isolated yields. As can be seen in Table 1, reaction of propionate ester **2a** with bidentate benzyloxyacetaldehyde proceeded with near complete *syn*-diastereoselectivity (98:2 ratio by HPLC; 400 MHz $^1H$ NMR revealed only one diastereomer, entry 1) with 80% isolated yield after silica gel chromatography.[6] Similarly, reaction with benzyloxypropionaldehyde (entry 2) also afforded aldol product with excellent *syn*-diastereoselectivity and isolated yields. In comparison, reaction with benzyloxybutyraldehyde (entry 3) furnished the *syn*-aldol product **5c** with slightly lower selectivity and yield. The reaction of hydrocinnamate derivative **2b** and 4-methylvalerate

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

| Aldehyde | Compd[a] | % Yield[b] | *Syn:Anti* (**5**/**4**)[c] |
|---|---|---|---|
| $BnOCH_2CHO$ | **5a** | 80 | 98 : 2 |
| $BnO(CH_2)_2CHO$ | **5b** | 81 | 97 : 3 |
| $BnO(CH_2)_3CHO$ | **5c** | 58 | 91 : 9 |
| $BnOCH_2CHO$ | **5d** | 63 | 97 : 3 |
| $BnOCH_2CHO$ | **5e** | 60 | 96 : 4 |
|  | **5f** | 84 | 99 : 1 |
|  | **4g** | 59 | 30 : 70[d] |

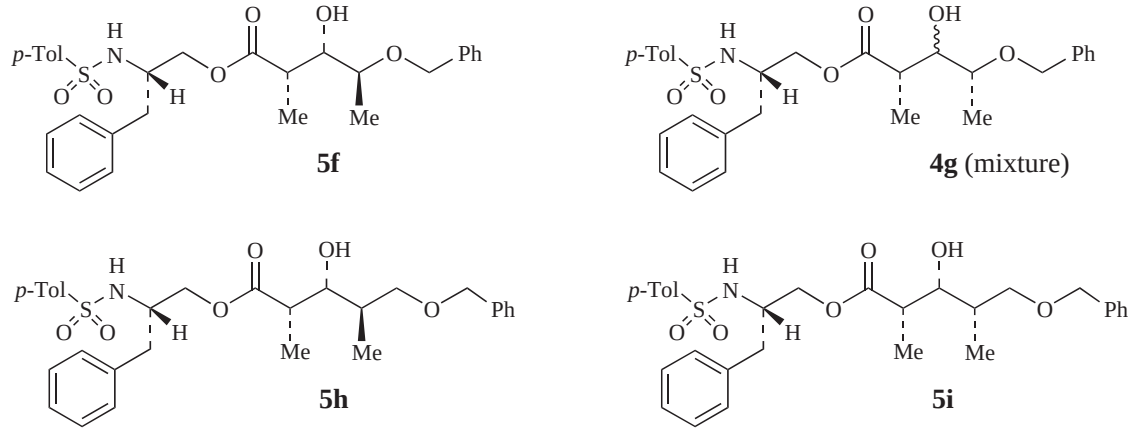



**Figure 1.**

derivative **2c** with benzyloxyacetaldehyde also proceeded with excellent *syn*-diastereoselectivities (entries 4 and 5).

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 **2a** (Fig. 1). Aldol reaction of the propionate ester **2a** 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 **5f** (entry 6) in 84% yield after silica gel chromatography. In a mismatched case, the reaction of **2a** and 2(*R*)-benzyloxypropionaldehyde, however, afforded a 30:70 mixture of (*syn*:*anti* ) isomers in 59% isolated yield (entry 7). Matched stereochemical effects are also evident in the aldol reaction of **2a** with 2(*R*)-methyl benzyloxypropionaldehyde (single diastereomer, entry 8). The corresponding reaction with 2(*S*)-methylbenzyloxypropionaldehyde (mismatched pair) also proceeded in good selectivity (83:17 mixture, entry 9).[7] In contrast, reaction of **2a** with monodentate aldehydes such as isovaleraldehyde and phenylpropargyl aldehyde provided the corresponding *anti*-isomer as the major product. However, *anti*-diastereoselectivity is significantly diminished compared to constrained 1-amino-2-indanol derived chiral auxiliary.[4a]

Saponification of the aldolates with aqueous lithium hydroxide in THF at 23°C for 2–3 h furnished the corresponding β-hydroxyacids (85–92% yield). Various aldolates were also converted to their corresponding alcohols **7** by lithium borohydride reduction in THF at 23°C for 2–4 h. In either case, the chiral auxiliary was fully recovered without loss of optical purity. The relative and absolute stereochemistry of various *syn* aldolates **5** were assigned by comparison of optical rotation, as well as $^1$H and $^{13}$C NMR spectra of the resulting acids or diols with literature values.[8] The transfer of chirality and observed diastereoselectivity can be rationalized by a Zimmerman–Traxler type transition state model **A** as postulated previously.[4,9] As shown in Fig. 2, the metallocycle adopts a chair-like conformation and chirality transfer proceeds through the sulfonamide bearing chiral center through effective metal chelation with the bidentate aldehydes.[10] Higher *syn*-selectivity for benzyloxyacetaldehyde or benzyloxypropionaldehyde as opposed to benzyloxybutyraldehyde is due to rigid five- or six-membered rather than flexible seven-membered metal chelation. Furthermore, the observed diastereoselectivities resulting from the double stereodifferentiating experiments are consistent with this model. As is evident in the model, the lack of *syn*-selectivity for the 2(*S*)-benzyloxypropionaldehyde is due to destabilizing non-bonded interaction between the methyl ($R_1$ = Me) group and the benzyl side chain of

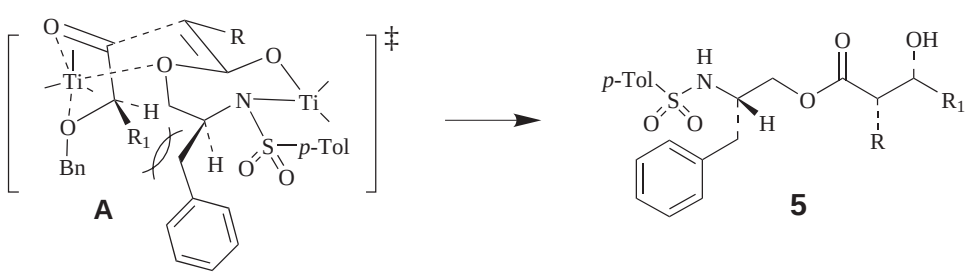



**Figure 2.**

the chiral template in the transition state. The choice of benzyl side chain in the chiral auxiliary is not critical since L-valinol derived propionyl ester enolate also provided comparable *syn*-diastereoselectivity (*syn*:*anti* ratio >99:1; 74% isolated yield) with benyloxyacetaldehyde under similar reaction conditions.

In conclusion, we devised a chelation controlled ester derived Ti-enolate based highly diastereoselective (82–98% de) *syn*-aldol reaction with bidentate oxyaldehydes. The methodology is convenient since inexpensive reagents and readily available optically active chiral auxiliaries were utilized. The scope of the reaction can also be extended to other bidentate aldehydes. Further studies including synthetic applications are in progress.

## Acknowledgements

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5. Our tentative assignment of the *Z*-enolate geometry is based upon a $^1$H NOESY ($CD_2Cl_2$) experiment in which a weak NOE was observed between the vinyl proton ($H_C$) and the methylene protons ($H_A$ and $H_B$). The absence of NOE between the vinyl methyl and the same methylene protons further supported this assignment. $^1$H NMR (**3**, R = Me, $CDCl_3$): $\delta$ 1.57 (d, 1H, $J$ = 7 Hz), 2.38 (s, 3H), 2.76 (dd, 1H, $J$ = 9.4, 13.6 Hz), 3.10 (dd, 1H, $J$ = 5.5, 13.6 Hz), 3.16 (dd, 1H, $J$ = 6.5, 8.5 Hz), 3.68 (dd, 1H, $J$ = 2.1, 8.5 Hz), 4.73 (q, 1H, $J$ = 7 Hz), 7.17–7.30 (m, 7H), 7.65 (d, 2H, $J$ = 8.2 Hz).
6. All new compounds gave satisfactory spectroscopic and analytical results. Preparation of *syn*-aldol **5a**: To a stirred solution of propionate ester **2a** (550 mg, 1.52 mmol) in $CH_2Cl_2$ (15 ml) at 0°C was added a 1 M solution of $TiCl_4$ (1.6 ml, 1.6 mmol) dropwise under a $N_2$ atmosphere. The resulting solution was stirred for an additional 15 min. To this solution was added *N*,*N*-diisopropylethylamine (0.8 ml, 4.6 mmol) in a dropwise manner. The mixture was stirred for 1 h at 0°C and then was warmed to 23°C. In a separate flask, to a stirred solution of benzyloxyacetaldehyde (457 mg, 3.04 mmol) in $CH_2Cl_2$ (20 ml) at −78°C under a $N_2$ atmosphere, was added a 1 M solution of $TiCl_4$ (3.2 ml, 3.2 mmol). After stirring for 10 min, the above enolate solution was added to this aldehyde solution dropwise via syringe over 8 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 twice 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 *syn* aldol product **5a** (620 mg, 80%) as a viscous oil. $[\alpha]_D^{23}$ −4.9 *c* 1.2, $CHCl_3$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$, 1.19 (d, 3H, $J$ = 7.1 Hz), 2.41 (s, 3H), 2.68 (m, 1H), 2.76 (d, 2H, $J$ = 7.2 Hz), 3.17 (d, 1H, $J$ = 4.0 Hz), 3.53 (d, 2H, $J$ = 5.8 Hz), 3.72 (m, 1H), 3.97–4.05 (m, 2H), 4.20 (m, 1H), 4.57 (dd, 2H, $J$ = 11.8, 20.5 Hz), 5.58 (d, 1H, $J$ = 8.1 Hz), 7.03–7.05 (m, 2H), 7.20–7.25 (m, 5H), 7.31–7.39 (m, 5H), 7.68 (d, 2H, $J$ = 8.3); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$, 11.5, 21.9, 38.9, 42.6, 54.5, 65.4, 71.1, 72.1, 73.8, 127.2, 127.4, 128.3, 128.9, 129.1, 129.7, 130.1, 136.9, 138.0, 138.3, 143.7, 175.1; IR (neat): 3508, 3282, 1731, 1328, 1159 cm$^{-1}$.

7. Mukaiyama aldol reactions of *N*-methylephidrine derived silyl ketene acetal and 2(*R*)- and 2(*S*)-methylbenzyloxypropionaldehyde have also exhibited similar *syn*-selectivities, see: Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754.
8. Optical rotation of corresponding carboxylic acids ($CHCl_3$ solvent for all), **6a**: $[\alpha]_D^{23}$ +11.93 (*c* 2.43), lit[4b]: $[\alpha]_D$ +12.97 (*c* 3.7); **6b**: $[\alpha]_D^{23}$ +13.6 (*c* 2.2), lit[4b]: $[\alpha]_D$ +9.44 (*c* 1.8); **6c**: $[\alpha]_D^{23}$ +28.6 (*c* 1.0), from Evans aldol: $[\alpha]_D^{23}$ +32 (*c* 0.53); **6f**: $[\alpha]_D^{23}$ +50 (*c* 0.5), from Evans aldol: $[\alpha]_D^{23}$ +50 (*c* 0.3); **7h**: $[\alpha]_D^{23}$ −43.5 (*c* 1.5), lit[7]: $[\alpha]_D$ −38.5 (*c* 1.0).
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10. The evidence of titanium chelation with the benzylether oxygen of oxyaldehydes is supported by the fact that $BF_3{\cdot}OEt_2$ instead of $TiCl_4$ for complexation of aldehydes resulted in very little *syn*-selectivity (*syn*:*anti* = 52:48). We are currently investigating the importance of sulfonamide functionality and its role in the transition state assembly.