Synthesis of Enantiomerically Pure Anti-Aldols: A Highly Stereoselective Ester-Derived Titanium Enolate Aldol Reaction

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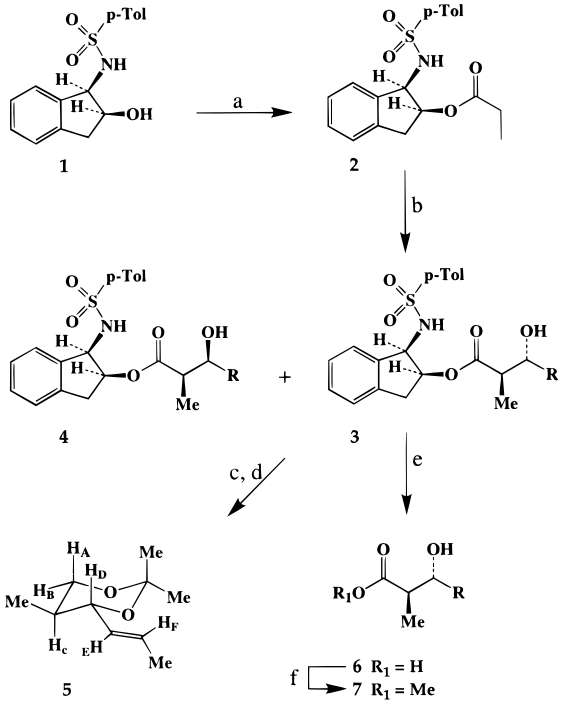
The aldol reaction leading to enantioselective construction of carbon−carbon bonds has emerged as an extremely powerful method in organic synthesis. In this context, a number of excellent synthetic methods have been developed over the years.[1] The control of both relative and absolute acyclic stereochemistry in aldol reactions can now be achieved in a highly stereoselective manner with a high degree of predictability. Such control has become particularly sophisticated in the synthesis of various syn-aldol products and is used widely.[2] We have recently reported that commercially available optically active *cis*-1-amino-2-indanol-derived oxazolidinones are highly effective chiral auxiliaries for syn-aldol reactions.[3] The corresponding enantioselective anti-aldol methodologies are currently an active area of research.[4] Herein, we report the development of a convenient *cis*-1-arylsulfonamido-2-indanol-derived titanium ester enolate based aldol reaction to provide anti-aldol products with excellent diastereoselectivity and isolated yields. Optically active *cis*-1-arylsulfonamido-2-indanols are readily accessible by sulfonylation of commercially available, enantiomerically pure *cis*-1-amino-2-indanols. The optically pure anti-α-methyl-*β*-hydroxy acids are conveniently obtained after removal of the chiral auxiliary under mild saponification conditions, and the chiral auxiliary is recovered without loss of optical purity.

The 1*R*,2*S*-chiral sulfonamide **1** was prepared (Scheme 1) by reaction with commercially available[5] optically active 1(*R*),2-(*S*)-*cis*-aminoindan-2-ol, *p*-toluenesulfonyl chloride (1 equiv), and triethylamine (3 equiv) in CH_2Cl_2 in the presence of a catalytic amount of DMAP at 23 °C for 12 h (85−92% yield). The acylation of hydroxy sulfonamide **1** with propionyl chloride (1.2 equiv) and triethylamine (3 equiv) in CH_2Cl_2 at 23 °C for 12 h afforded the propionate ester **2** (mp 106 °C; α^{23}_D +86°, *c* 0.98, $CHCl_3$) after silica gel chromatography (91% yield). The titanium enolate of **2** was generated by reaction with 1.2 equiv of $TiCl_4$ in CH_2Cl_2 at 0−23 °C for 15 min followed by addition of 4 equiv of *N*-ethyldiisopropylamine at 23 °C and stirring of the resulting brown solution for 1 h.[6,7] The ^{1}H-NMR (400 MHz) studies of the titanium enolate generated in a mixture of $CDCl_3$ and CH_2Cl_2, as described above, established that the enolization is complete under these conditions, providing a single enolate presumably with *Z*-geometry.[8] The titanium enolate thus generated was reacted with 2 equiv of butyraldehyde or isobutyraldehyde at −78 to 23 °C for several hours; interestingly, however, no aldol product was obtained, and the starting propionate ester **2** was recovered unchanged. However, the reaction of the above titanium enolate with various aldehydes precomplexed with $TiCl_4$ proceeded with good to excellent diastereoselectivities and isolated yields. The reactions are typically carried out by addition of the above titanium enolate to a solution of 2 equiv of aldehyde precomplexed with 2.4 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C followed by stirring the resulting mixture for 1 h and workup with aqueous NH_4Cl

Scheme 1[a]



[a] Key: (a) CH_3CH_2COCl, Et_3N, CH_2Cl_2, 23 °C; (b) $TiCl_4$, *i*Pr_2NEt, 23 °C then RCHO and $TiCl_4$, CH_2Cl_2, −78 °C; (c) $LiAlH_4$, THF, 0−23 °C; (d) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 23 °C; (e) LiOH, THF−H_2O, 23 °C; (f) CH_2N_2, Et_2O, 23 °C.

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(6) While alkyl esters are known[7a] to be not enolizable with $TiCl_4/Et_3N$, formation of titanium enolate from esters through internal chelation with the sulfonamido group has been reported; see: Xiang, Y.; Olivier, E.; Ouimet, N.; *Tetrahedron Lett.* **1992**, *33*, 457.

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(8) ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* 7.78 (d, 2 H, *J* = 8.3 Hz), 7.16−7.35 (m, 6 H), 5.55 (d, 1 H, *J* = 5.7 Hz), 4.67 (q, 1 H, *J* = 7 Hz), 4.28 (m, 1 H), 3.05−3.14 (m, 2 H), 2.50 (s, 3 H), 1.51 (d, 3 H, *J* = 7.0 Hz).

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Table 1. Aldol Reaction of Propionate Ester **2** with Representative Aldehydes

entry	aldehyde	% yield[a]	anti:syn (**3**/**4**)[b]
1	MeCHO	50[c]	85:15
2	EtCHO	50	85:15
3	*n*PrCHO	74	95:5
4	*i*PrCHO	91	85:15
5	*i*BuCHO	97	>99:1
6	MeCH=CHCHO	41	95:5
7	PhCHO	85	45:55
8	$PhCH_2CH_2CHO$	44	96:4
9	PhCH=CHCHO	63	99:1

[a] Isolated yield of both isomers after silica gel chromatography. Time = 1 h. [b] Diastereomeric ratios were determined by ^{1}H-NMR and HPLC. [c] Isolated anti-isomer only.

solution. The results are summarized in Table 1. The ester enolate aldol reaction with a variety of conjugated and non-conjugated aldehydes proceeded with excellent anti-diastereoselectivity except in the case of benzaldehyde, which did not exhibit any selectivity.[9] The diastereomeric mixture ratio was determined by ^{1}H-NMR (400 MHz) as well as by HPLC analysis of the aldol products prior to chromatography. Aldol reaction with butyraldehyde (entry 3) afforded an anti-diastereoselectivity of 95:5. Both anti- and syn-isomers could be separated by silica gel chromatography (74% combined yield). The reaction with isovaleraldehyde proceeded with almost complete anti-diastereoselectivity (>99% de by HPLC; 400 MHz ^{1}H-NMR revealed only one diastereomer) with 97% isolated yield after silica gel chromatography. Similarly, the reaction with conjugated aldehydes also provided excellent anti-diastereoselectivity.[10]

In order to establish the relative stereochemistry, the anti-isomer **3** derived from crotonaldehyde (entry 6) was converted to the isopropylidene derivative **5** by reduction with LAH in THF at 0 °C followed by exposure of the resulting diol to dimethoxypropane in CH_2Cl_2 in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate. The ^{1}H-NMR (400 MHz) analysis of **5** firmly established the identity of the anti-isomer in this chiral ester enolate based aldol reaction. Of particular interest, a coupling constant (J_{CD}) of 10.1 Hz was measured between the H_C and H_D protons of **5**.[11] The absolute configurations of the new asymmetric centers of **3** were assigned after removal of the chiral sulfonamides, conversion of the resulting anti-α-methyl-*β*-hydroxy acids to the corresponding methyl ester, and comparison of the optical rotations of the resulting **7** with literature values.[4a] For example, treatment of the isobutyraldehyde-derived anti-aldol product (entry 4) with aqueous lithium hydroxide in THF at 23 °C for 2 h afforded the corresponding acid which was converted to optically pure methyl ester **7** (α^{23}_D −14.2°, *c* 1.04, $CHCl_3$; lit.[4a] α^{23}_D −12.5°, *c* 1.04, $CHCl_3$) with an excess of diazomethane in diethyl ether. The chiral sulfonamide **1** was recovered (95% after silica gel chromatography) after saponification without loss of optical purity (α^{23}_D −34°, *c* 1.5, $CHCl_3$). Similarly, the butyraldehyde-derived anti-aldol product was converted to the optically pure methyl ester **7** (α^{23}_D −4°, *c* 2.0, $CHCl_3$; lit.[4a] α^{23}_D −2.5°, *c* 1.03, $CHCl_3$). The relative and absolute stereochemistries of the isobutyraldehyde-derived syn-aldol product **4** (entry 4) were established by comparison of ^{1}H-NMR (400 MHz) and optical rotation of **4** with an authentic sample prepared utilizing Evan's boron enolate based syn-aldol reaction.[2a] The assignment of stereochemistry for other syn-aldol products was made on the basis of comparisons of ^{1}H-NMR spectra.

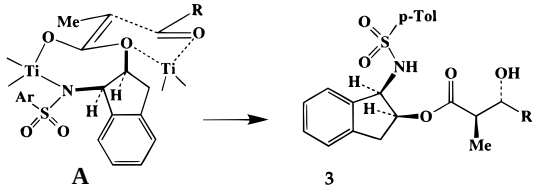

Figure 1.

The high degree of stereoselection associated with this current asymmetric anti-aldol process could be rationalized by a Zimmerman−Traxler type transition state model **A** (Figure 1).[12] The model is derived based on the following assumptions: (1) the geometry of the titanium enolate is *Z*; (2) the titanium enolate is a seven-membered metallocycle with a chairlike conformation; (3) a second titanium metal is involved in the transition state where it is chelated to indanyloxy oxygen as well as to the aldehyde carbonyl in a six-membered chairlike transition state. The involvement of two titanium metal atoms is supported by the fact that the titanium enolate derived from **2** does not react with aldehydes without precomplexation with $TiCl_4$. The above transition state model accounts for the observed stereoselection except in the case of benzaldehyde, which has shown no selectivity. While this model explains much of the present stereoselection, the evidence of such a model requires further experimentation which is currently in progress.

In summary, the present chiral ester derived titanium enolate aldol reaction with various aldehydes represents a highly effective synthetic protocol for providing anti-aldol products with high levels of diastereo- and enantioselectivity. The generality of the current anti-selective aldol process has been demonstrated with nine different aldehydes. Since both enantiomers of *cis*-1-arylsulfonamido-2-indanol are readily prepared from the commercially available optically active *cis*-1-amino-2-indanols, the present anti-aldol methodology provides a convenient access to either anti-aldol enantiomer with high optical purity. Mechanistic investigations as well as synthetic applications of the current anti-aldol methodology are the subject of ongoing research in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for aldols and their derived *β*-hydroxy acids (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) When the aldol reaction was carried out with a 1:1 mixture of benzaldehyde and isovaleraldehyde, the ^{1}H-NMR of crude products revealed the presence of a 65:35 ratio of anti/syn-diastereomers of benzaldehyde and a single anti-isomer of isovaleraldehyde as seen in entry 5.

(10) All new compounds gave satisfactory spectroscopic and analytical results.

(11) ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.73 (dq, 1 H, J = 6.5, 15.3 Hz, $\mathbf{H_F}$), 5.38 (ddd, 1 H, J = 1.3, 7.7, 15.3 Hz, $\mathbf{H_E}$), 3.84 (dd, 1 H, J = 8.1, 10.1 Hz, $\mathbf{H_D}$), 3.73 (dd, 1 H, J = 5.1, 11.7 Hz, $\mathbf{H_B}$), 3.54 (dd, 1 H, J = 11.5, 11.5 Hz, $\mathbf{H_A}$), 1.72 (dd, 3 H, J = 1.3, 6.5 Hz), 1.66 (m, 1 H, He), 1.47 (s, 3 H), 1.41 (s, 3 H), 0.7 (d, 3 H, J = 6.8 Hz).

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