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# Stereoselective Chloroacetate Aldol Reactions: Syntheses of Acetate Aldol Equivalents and Darzens Glycidic Esters

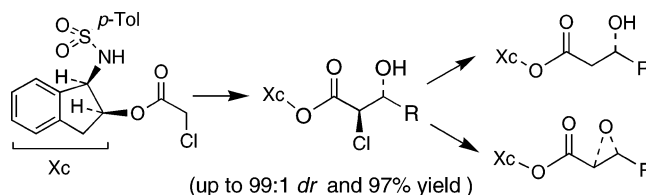
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Received May 18, 2004

## ABSTRACT



Aldol reaction of the Ti-enolate derived from *cis*-1-tosylamido-2-indanyl chloroacetate with representative aldehydes proceeded in excellent yield and high diastereoselectivities. Removal of chlorine provided alternative access to highly diastereoselective acetate aldol equivalents or the corresponding glycidic ester condensation products.

Enantioselective synthesis of *anti*- or *syn*- $\alpha$ -halo- $\beta$ -hydroxy carbonyl units is of considerable interest since this structural feature can provide access to a variety of useful intermediates. Asymmetric aldol reaction of chloroacetate derivatives appeared to be the most direct route to these intermediates; however, reports of  $\alpha$ -halo acetate aldol reactions are rather limited.<sup>1</sup> Furthermore, most reported methodologies are based upon *syn*-aldol reactions of haloacetate derivatives.<sup>1,2</sup> The corresponding *anti*-selective  $\alpha$ -halo acetate aldol reaction has thus far been very rare. Numerous halo-aldolates have already been utilized in syntheses, including their transformation into  $\alpha$ -amino- $\beta$ -hydroxy derivatives,<sup>2</sup> as well as in the synthesis of acetate aldol equivalents.<sup>3</sup> In addition,  $\alpha$ -chloro- $\beta$ -hydroxy aldolates are precursors to Darzens condensation products leading to  $\alpha,\beta$ -epoxycarbonyl derivatives, which are impor-

tant subunits of taxol and taxostere.<sup>4</sup> In continuing our studies aimed at developing practical methodologies utilizing ester-derived Ti-enolate aldol reactions, we have investigated asymmetric *syn*- and *anti*-aldol reactions of chloroacetate derivatives. Herein we report that reactions of chiral sulfonamido chloroacetate-derived titanium enolates with a variety of monodentate and bidentate aldehydes provided highly diastereoselective *anti*- and *syn*- $\alpha$ -chloro- $\beta$ -hydroxy carbonyl derivatives, respectively. Additive effects on *anti* diastereoselectivity with monodentate aldehydes are noteworthy. Various aldolates were obtained in excellent diastereoselectivities (up to 99% *dr*) and isolated yields. Aldolates so formed were converted to optically active acetate aldol derivatives and  $\alpha,\beta$ -epoxy esters, the corresponding Darzens condensation product under mild reaction conditions.

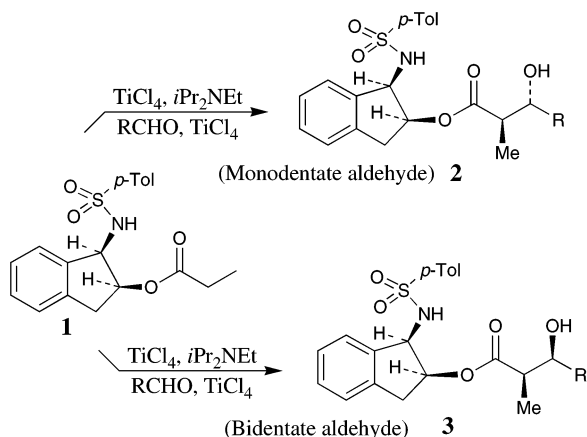
We recently reported *cis*-1-tosylamido-2-indanyl propionate-derived titanium enolate aldol reactions of monodentate and bidentate aldehydes providing highly diastereoselective

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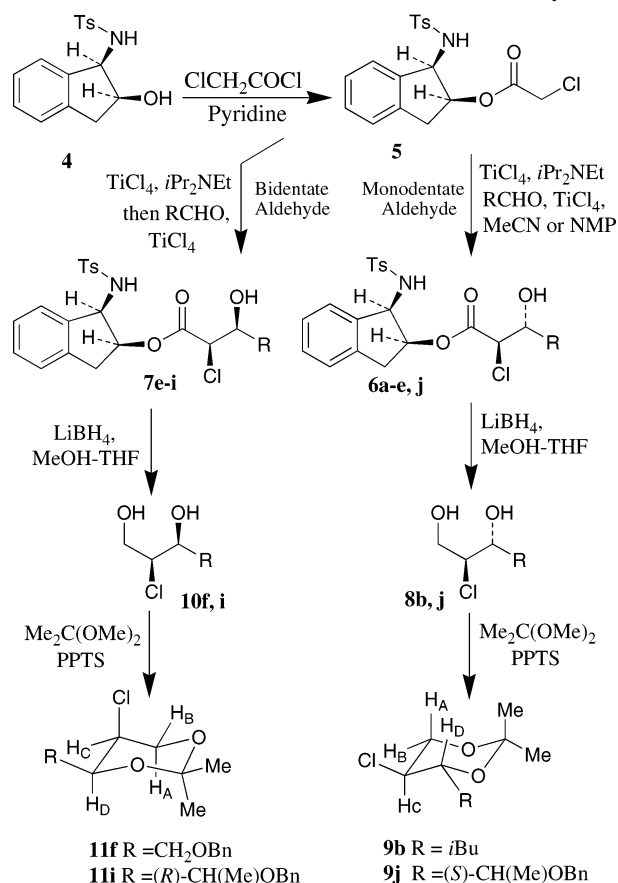
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**Figure 1.** Ester-derived Ti-enolate aldol reaction.

*anti*- and *syn*-aldol products, respectively (Figure 1).<sup>5</sup> Subsequently, we speculated that the corresponding  $\alpha$ -chloro acetate-derived enolate would provide a similar degree of diastereoselectivity under similar reaction conditions. Thus, (1*R*,2*S*)-1-tosylamido-2-indanol **4**<sup>5</sup> was treated with chloroacetyl chloride and pyridine in  $\text{CH}_2\text{Cl}_2$  at 0 °C for 2 h to furnish  $\alpha$ -chloro acetate **5** in 96% yield (Scheme 1). In a preliminary experiment, **5**-derived Ti-enolate (generated from 1.1 equiv of  $\text{TiCl}_4$  and 2.5 equiv of Hunig's base at 0 °C) was reacted with isobutyraldehyde precomplexed with  $\text{TiCl}_4$  (2.2 equiv) at -78 °C for 2 h. This provided a mixture of aldol products in 82% yield with the *anti* isomer as the major product (*anti*:*syn* ratio 75:25). Out of four possible diastereomers, only formation of *anti* diastereomer **6a** ( $\text{R} = i\text{Pr}$ ) and *syn* diastereomer **7a** ( $\text{R} = i\text{Pr}$ ) was observed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR analysis. The *anti* diastereoselectivity is significantly lower than the corresponding propionate derivative.<sup>5a</sup> To further improve *anti* diastereoselectivity, we investigated the effects of additives on *anti* diastereoselectivity with a range of additives, and the results are shown in shown Table 1. As can be seen, acetonitrile and *N*-methyl pyrrolidinone (NMP) showed significant effects on *anti* diastereoselectivities and yields (entries 2 and 3). Optimum results were observed with 2.2 equiv of additive. Reaction of isobutyraldehyde in the presence of 1 equiv of  $\text{CH}_3\text{CN}$  provided significantly lower *anti* diastereoselectivity (entry 4) compared to 2.2 equiv of  $\text{CH}_3\text{CN}$  (entry 2). We have recently observed similar additive effects leading to improved *anti*-aldol reaction of the Ti-enolate derived from *cis*-2-arylsulfonamido-1-acenaphthenyl propionate.<sup>6</sup> Additive effects with  $\text{PPh}_3$ , NMP, and THF in titanium-mediated aldol reactions have been investigated by others as well.<sup>7</sup> A representative reaction (entry 2) in Table 1 with  $\text{CH}_3\text{CN}$  as an additive was carried out as follows: Ti-enolate of  $\alpha$ -chloro acetate was formed by reaction of **5** with  $\text{TiCl}_4$  (1.1 equiv)

**Scheme 1.** Ti-Enolate Aldol Reactions with Aldehydes



at 0 °C for 5 min followed by further treatment with *N,N*-diisopropylethylamine (2.5 equiv) at 0 °C for 1 h. The resulting titanium enolate was added to a precomplexed mixture of isobutyraldehyde (2 equiv),  $\text{TiCl}_4$  (2.2 equiv), and  $\text{CH}_3\text{CN}$  (2.2 equiv) at -78 °C. The resulting mixture was stirred at that temperature for 2 h prior to quenching with aqueous  $\text{NH}_4\text{Cl}$ . This reaction protocol was equally effective when the reaction was carried out on a multigram scale. Aldol reactions with other additives in Table 1 were carried out using an analogous procedure. While additive effects of  $\text{Ph}_3\text{P}$ , HMPA, and THF (entries 5, 8, and 9) resulted in

**Table 1.** Additive Effect on Aldol Reaction with *iPrCHO*

entry	additives	equiv	yield <sup>a</sup>	<i>anti</i> : <i>syn</i> <sup>b</sup>
1	none	0	82	75:25
2	$\text{CH}_3\text{CN}$	2.2	66	98:2
3	NMP	2.2	71	94:6
4	$\text{CH}_3\text{CN}$	1.0	60	88:12
5	$\text{Ph}_3\text{P}$	2.2	22	99:1
6	$\text{NC}(\text{CH}_2)_2\text{CN}$	1.1	64	93:7
7	$(\text{CH}_3)_3\text{CCN}$	2.2	44	91:9
8	HMPA	2.2	17	99:1
9	THF	2.2	15	99:1

<sup>a</sup> Isolated yield of diastereomeric mixtures. <sup>b</sup> Ratio determined by  $^1\text{H}$  NMR before chromatography.

(5) (a) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527.  
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(6) Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2003**, *5*, 1063.

**Table 2.** Aldol Reactions with Representative Aldehydes

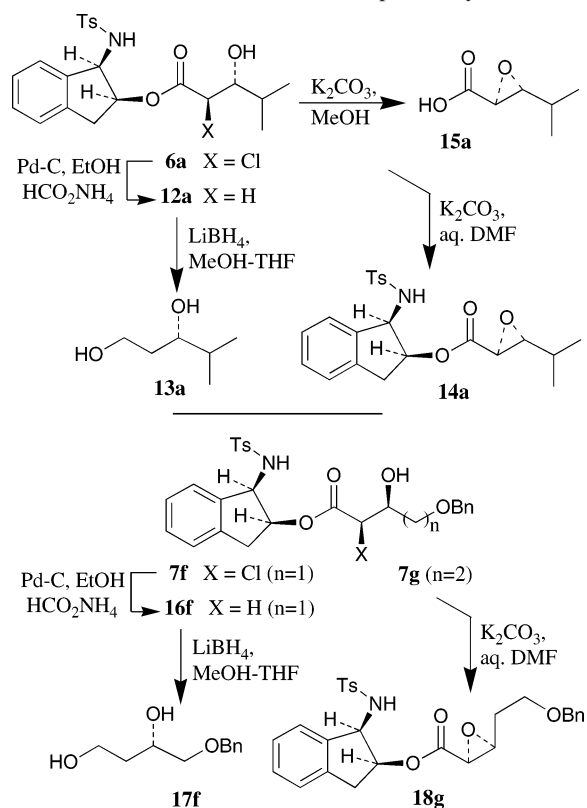
entry	aldehyde	major product	yield <sup>a</sup>	anti ( <b>6</b> ):syn ( <b>7</b> ) <sup>b</sup>
1	<i>i</i> BuCHO	<b>6b</b>	88 <sup>c</sup>	99:1
2	<i>i</i> BuCHO	<b>6b</b>	90 <sup>d</sup>	99:1
3	BuCHO	<b>6c</b>	68 <sup>c</sup>	96:4
4	BuCHO	<b>6c</b>	70 <sup>d</sup>	96:4
5	PrCHO	<b>6d</b>	79 <sup>c</sup>	96:4
6	PrCHO	<b>6d</b>	60 <sup>d</sup>	97:3
7	PhCHO	<b>6e</b>	62 <sup>c</sup>	96:4
8	PhCHO	<b>6e</b>	47 <sup>d</sup>	96:4
9	PhCHO	<b>7e</b>	64	10:90
10	BnOCH <sub>2</sub> CHO	<b>7f</b>	86	1:99
11	BnO(CH <sub>2</sub> ) <sub>2</sub> CHO	<b>7g</b>	79	4:96
12	BnO(CH <sub>2</sub> ) <sub>3</sub> CHO	<b>7h</b>	82 <sup>e</sup>	26:74
13	( <i>R</i> )-BnOCH-(Me)CHO	<b>7i</b>	94	1:99
14	( <i>S</i> )-BnOCH-(Me)CHO	<b>6j</b>	82	99:1
15	(±)-BnOCH-(Me)CHO	<b>7i</b>	95 <sup>e</sup>	5:95

<sup>a</sup> Isolated yield of pure diastereomer. <sup>b</sup> Ratio determined by <sup>1</sup>H NMR before chromatography. <sup>c</sup> CH<sub>3</sub>CN (2.2 equiv) was used as an additive. <sup>d</sup> NMP (2.2 equiv) was used as an additive. <sup>e</sup> Isolated yield of diastereomeric mixtures.

excellent anti diastereoselectivities, reaction yields are far from satisfactory. Also, systematic attempts to improve reaction yields have been unsuccessful thus far.

The scope and utility of chloroacetate aldol reactions in the presence of CH<sub>3</sub>CN or NMP as additive were then investigated with a range of representative monodentate and bidentate aldehydes. The results are shown in Table 2. As it turned out, the chloroacetate aldol reactions with monodentate aliphatic aldehydes proceeded with excellent anti selectivities and good to excellent yields (entries 1–6). Interestingly, reaction with benzaldehyde, in the presence of either CH<sub>3</sub>CN or NMP as an additive showed good anti diastereoselectivity (entries 7 and 8). However, the corresponding reaction in the absence of additive displayed syn diastereofacial selectivity (entry 9). Consistent with our previous observation with propionate aldol reactions, bidentate oxyaldehydes such as benzyloxy acetaldehyde and benzyloxypropionaldehyde exhibited excellent syn diastereoselectivities and yields (entries 10 and 11) without any additive. Reaction of benzyloxyacetaldehyde in the presence of 2 equiv of CH<sub>3</sub>CN as an additive provided no change in syn diastereoselectivity, but the aldol product was obtained in only 37% yield.

Furthermore, we have investigated double asymmetric induction employing 2(*R*)- and 2(*S*)-benzyloxypropionaldehyde. In the matched case, aldol reaction with 2(*R*)-benzyloxypropionaldehyde provided only a single syn diastereomer **7i** in excellent yield (entry 13). However, for the mismatched case, aldol reaction with 2(*S*)-benzyloxypropionaldehyde exclusively afforded an *anti*-aldol adduct **6j** (entry

**Scheme 2.** Acetate Aldol and Epoxide Synthesis

14). On the basis of these results, we performed kinetic resolution experiments with racemic 2-benzyloxypropionaldehyde. The aldol reaction was carried out with 2 equiv of racemic aldehyde for 30 min to provide a 95:5 syn diastereomeric ratio in 95% yield (entry 15). Formation of major syn diastereomer **7i** resulted from preferential reaction with matched 2(*R*)-benzyloxypropionaldehyde. Recovered 2(*S*)-benzyloxypropionaldehyde showed 98.7% enantiomeric excess and 40% recovered yield.<sup>8</sup>

The relative stereochemistry of aldol products was assigned on the basis of comparison of observed vicinal coupling constants of the major aldol products ( $J_{2,3} = 6\text{--}10$  Hz for *anti*-aldols and  $J_{2,3} = 3\text{--}4$  Hz for *syn*-aldols) with the corresponding propionate aldol products.<sup>10</sup> Further confirmation of the relative stereochemistry of *anti*-aldols **6b–j** and *syn*-aldols **7e–i** was established by their conversion to the corresponding isopropylidene derivatives (**9** and **11**) and comparison of coupling constants with the literature values as described by us previously.<sup>6</sup> For synthesis of isopropylidene derivatives, aldolates were treated with LiBH<sub>4</sub> in a mixture of THF and methanol at 23 °C to provide chlorohydrins **8** and **10**. Exposure of chlorohydrins **8** and **10** to

(7) For previous investigations with PPh<sub>3</sub>, NMP, and THF as additives, see: (a) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna G. *J. Org. Chem.* **1987**, *52*, 2754. (b) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (d) Shirokar, S.; Nerz-Stormes, M.; Thorntorn, E. R. *Tetrahedron Lett.* **1990**, *31*, 4699.

(8) Enantiomeric excess was calculated from comparison of the observed optical rotation value with the reported value ( $[\alpha]_D^{20} -51.5$  (c 0.89, CHCl<sub>3</sub>); lit.<sup>9</sup>  $[\alpha]_D^{20} -52.2$  (c 6.5, CHCl<sub>3</sub>)).

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(10) (a) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; John, J. E.; Lampe, J. J. *J. Org. Chem.* **1980**, *45*, 1066.

dimethoxypropane in CH<sub>2</sub>Cl<sub>2</sub> in the presence of a catalytic amount of PPTS furnished isopropylidene derivatives **9** and **11**, respectively.

The absolute configuration of the aldolates was established after their conversion to the corresponding  $\alpha,\beta$ -epoxy acid and 1,3-diols and comparison of optical rotation with the literature. Treatment of aldolate **6a** with K<sub>2</sub>CO<sub>3</sub> in methanol at 23 °C effected removal of the chiral auxiliary and concomitant formation of  $\alpha,\beta$ -epoxy acid **15a** in 70% yield. Catalytic hydrogenation of **6a** over Pd–C in the presence of ammonium formate afforded dechlorination product **12a**. Reduction of **12a** with LiBH<sub>4</sub> furnished alcohol **13a**. Optical rotations and spectroscopic data of alcohols **13a**, **17f**, and acid **15a** were compared with literature values.<sup>11</sup> When the aldolates were treated with K<sub>2</sub>CO<sub>3</sub> in aqueous DMF at 23 °C, the corresponding  $\alpha,\beta$ -epoxy esters were formed.<sup>15</sup> Furthermore, catalytic dechlorination of aldolates **6a,b** and

**7f,i** afforded the corresponding acetate aldol equivalents in excellent yields. The stereochemical outcome of chloroacetate aldol reactions to provide anti diastereoselectivities with monodentate aldehydes and syn selectivities with bidentate aldehydes is consistent with our previous stereochemical models.<sup>5</sup> Presumably, the additive provides more steric bias on the titanium metal center, inducing improved anti selectivity with monodentate aldehydes.

In summary, we have developed highly diastereoselective titanium enolate-based *anti*- and *syn*-aldol reactions with chiral  $\alpha$ -chloro acetate derivatives. Pronounced additive effects resulted in improved anti selectivity with monodentate aldehydes. The ready availability of the chiral auxiliary and the use of Ti-reagent renders this methodology very useful.

**Acknowledgment.** Financial support by the National Institutes of Health is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures, spectral data for compounds **5–18**, and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for compounds **5–18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) **15a**: [ $\alpha$ ]<sub>D</sub><sup>23</sup> 11.4 (*c* 0.71, 95% EtOH); lit.<sup>12</sup> *ent*-**15a** [ $\alpha$ ]<sub>D</sub><sup>23</sup> –15.2 (*c* 0.52, 95% EtOH). **13a**: [ $\alpha$ ]<sub>D</sub><sup>23</sup> –18 (*c* 0.5, CHCl<sub>3</sub>); lit.<sup>13</sup> [ $\alpha$ ]<sub>D</sub> –11.3 (*c* 2, CHCl<sub>3</sub>). **17f**: [ $\alpha$ ]<sub>D</sub><sup>23</sup> 8.98 (*c* 0.88, MeOH); lit.<sup>14</sup> [ $\alpha$ ]<sub>D</sub> 7.66 (*c* 1.75, MeOH).

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(14) Takano, S.; Kasahara, C.; Ogasawara, K. *Chem. Lett.* **1983**, 175.

(15) Yields for **14a**, **14b**, and **18g** were 58, 65, and 49%, respectively.