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Highly Selective Acetate Aldol Additions Using Mesityl-Substituted Chiral Auxiliaries

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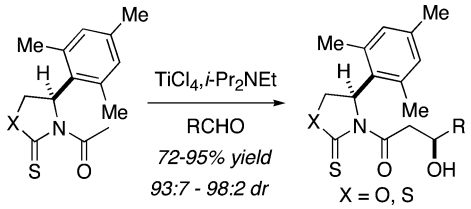
ABSTRACT



Highly diastereoselective acetate aldol additions using chlorotitanium enolates of mesityl-substituted *N*-acetyloxazolidinethione and *N*-acetylthiazolidinethione auxiliaries are reported. These additions proceed in high yields and diastereoselectivities (93:7 to 98:2) for aliphatic, aromatic, and α,β-unsaturated aldehydes. Double diastereoselective acetate aldol additions are also reported and are found to proceed in high yields and diastereoselectivities (90:10 to 97:3).

On the basis of the seminal report of Evans and co-workers on the use of boron enolates of *N*-acyloxazolidinones for highly diastereoselective *syn*-propionate aldol additions,[1] auxiliary mediated asymmetric aldol additions have become one of the most valuable methods for the construction of carbon−carbon bonds.[2] In particular, the asymmetric aldol addition has played a significant role in the synthesis of the β-hydroxycarbonyl subunit, prevalent in polyketide-derived natural products.[3] Previous work in our laboratory has led to the development of highly diastereoselective auxiliary-based propionate aldol additions[4] and *anti*-selective glycolate aldol additions through the use of chlorotitanium enolates of *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones.[5]

The development of an analogous method toward an auxiliary-based asymmetric acetate aldol addition[6] has proven to be a more difficult task; the same auxiliaries that have been successful for other types of aldol additions result in reduced diastereoselectivity for the acetate aldol addition, particularly with aliphatic aldehydes.[1] A number of methods have been reported for acetate-type aldol additions involving the use of tin,[7] lithium,[8] boron,[9] and titanium[10] based acetate

(1) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(2) For selected reviews, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917. (c) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(3) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(4) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.

(5) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591.

(6) For reviews on the asymmetric acetate aldol addition, see: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1. (b) Braun, M. *Angew. Chem., Int. Ed.* **1987**, *26*, 24.

(7) (a) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Inoue, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418. (b) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

(8) (a) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. (b) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3378.

(9) (a) Yan, T. H.; Hung, A. W.; Lee, H. C.; Chang, C. S. *J. Org. Chem.* **1994**, *59*, 8187. (b) Zhang, Y. C.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23. (c) Zhang, Y. C.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 3139.

(10) (a) Yan, T. H.; Hung, A. W.; Lee, H. C.; Chang, C. S.; Liu, W. H. *J. Org. Chem.* **1995**, *60*, 3301. (b) Gonzalez, A.; Aiguade, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949. (c) Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, *4*, 2253.

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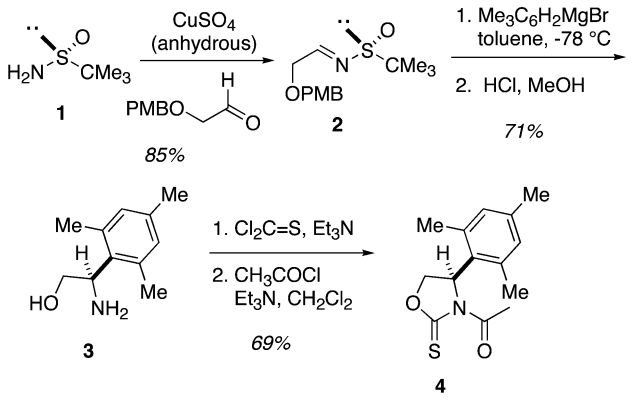
enolates. These methods often rely on the use of reagents and metals that are expensive or difficult to handle and often suffer from narrow substrate scopes and modest diastereoselectivities, further limiting the utility of the asymmetric acetate aldol addition in synthetic applications. The highly hindered auxiliaries recently advanced by Phillips[10c] and Sammakia[9b,c] provide the most consistent high levels of diastereoselectivity to date.

The diminished diastereoselectivity of the acetate aldol additions in comparison to the high level of diastereoselectivity attainable for propionate aldol additions has been attributed to the lack of substitution at the α-carbon of the enolate, which is believed to function as an important stereocontrol element. In an attempt to overcome this issue, we have investigated more sterically encumbered chiral auxiliaries to improve the selectivity in acetate aldol additions of chlorotitanium enolates of *N*-acetylthiazolidinethiones. Mesityl-substituted oxazolidinethione and thiazolidinethiones were chosen due to the restricted rotational freedom about the bond between the aromatic ring and the benzylic carbon.[11] We herein report the synthesis of mesityl-substituted *N*-acetyloxazolidinethione and *N*-acetylthiazolidinethiones and the use of their chlorotitanium enolates in acetate aldol additions.

Initial efforts focused on the development of mesityl-substituted *N*-acetyloxazolidinethione **4**. Oxazolidinethione **4** was synthesized using *t*-butylsulfinamide methodology developed by Ellman (Scheme 1).[12] Imine **2** was prepared

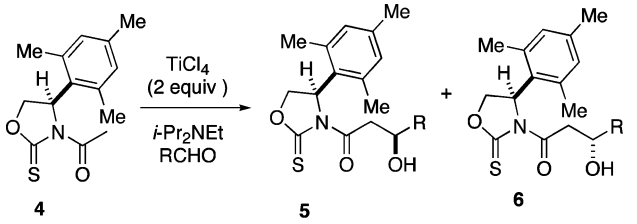
Scheme 1



via the $CuSO_4$-mediated condensation of (*R*)-(+)-2-methyl-2-propanesulfinamide (**1**)[13] and (4-methoxybenzyloxy)-acetaldehyde. Addition of mesitylmagnesium bromide to imine **2** afforded a single diastereomer of the protected amino alcohol. Concomitant acid-catalyzed removal of the sulfinyl and PMB groups provided amino alcohol **3**. Finally, formation of the auxiliary followed by acylation yielded (*R*)-*N*-acetyloxazolidinethione **4**.[14]

Treatment of **4** with $TiCl_4$ (2 equiv) and diisopropylethylamine (2 equiv) in CH_2Cl_2 at −78 °C, followed by addition of the aldehyde (1.2 equiv), resulted in a highly diastereoselective acetate aldol addition, utilizing a series of aldehydes (Table 1).[15] This protocol is amenable to aliphatic, aromatic,

Table 1. Aldol Additions of Oxazolidinethione **4**



entry	aldehyde	yield (%)[a]	dr (**5**/**6**)[b]
1	PhCH=CHCHO	72	93:7
2	$(CH_3)_2CHCH_2CHO$	84	96:4
3	PrCHO	85	95:5
4	$(CH_3)_2CHCHO$	88	94:6
5	EtCHO	78	95:5
6	PhCHO	89	96:4

[a] Combined yield of diastereomers after purification. [b] Obtained by HPLC analysis of crude reaction mixtures.

and α,β-unsaturated aldehydes. The stereochemistry of the addition was determined by reductive cleavage of the adduct obtained in entry 4 to afford (*S*)-4-methyl-pentane-1,3-diol.[16]

Efforts then shifted toward the formation of mesityl-substituted *N*-acetylthiazolidinethione **9** (Scheme 2). A major advantage of using thiazolidinethiones over oxazolidinethiones lies in the ease with which thiazolidinethiones can be directly converted to a variety of functional groups, such as aldehydes, amides, β-ketophosphonates, and β-ketoesters, whereas conversions of oxazolidinethiones are limited.[17,4b] All attempts, however, to convert amino alcohol **3** into a

(11) (a) Medina, E.; Moyano, A.; Pericas, M. A.; Riera, A. *Helv. Chim. Acta* **2000**, *83*, 972. (b) Bandini, M.; Cozzi, P. G.; Gazzano, M.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2001**, *10*, 1937.

(12) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772. (c) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *119*, 9913.

(13) (*R*)-(+)-2-Methyl-2-propanesulfinamide and (*S*)-(−)-2-methyl-2-propanesulfinamide are commercially available but can also be synthesized via Ellman's procedure: Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157.

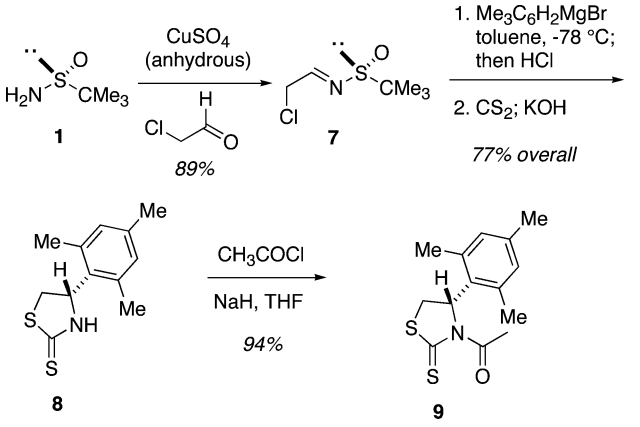
(14) (*S*)-*N*-Acetyloxazolidinethione can be accessed from the same sequence of steps, starting from (*S*)-(−)-2-methyl-2-propanesulfinamide.

(15) **Typical aldol procedure using *N*-acetyloxazolidinethione 4:** To a dry 25 mL round-bottom flask, under argon, was added *N*-acetyloxazolidinethione (0.263 g, 1.00 mmol) and 5 mL of CH_2Cl_2 (0.2 M). The flask was cooled to −40 °C. Titanium tetrachloride (neat, 0.22 mL, 2.00 mmol) was added, and the reaction mixture was stirred for 5 min. Diisopropylethylamine (0.35 mL, 2.00 mmol) was then added. The solution was stirred for 2 h at −40 °C and was then cooled to −78 °C, whereupon the freshly distilled aldehyde (neat, 1.2 mmol) was added. The mixture was stirred for 4 h at −78 °C, then quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/Hex). Yields and diastereoselectivities are listed in Table 1.

(16) (*S*)-4-Methyl-pentane-1,3-diol: $[\alpha]_D = -17.0°$ ($c = 0.25$, $CHCl_3$). For the lit. value of (*R*)-4-methyl-pentane-1,3-diol, see: (a) ref 10c. (b) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A. *J. Org. Chem.* **1992**, *57*, 1412.

(17) Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 555.

Scheme 2

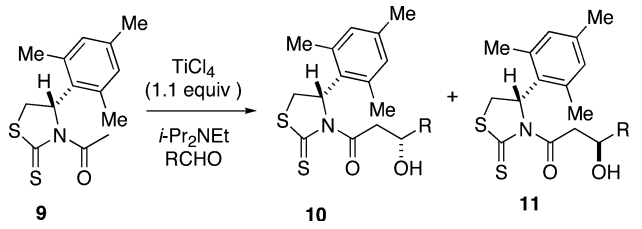


mesityl-substituted thiazolidinethione using Le Corre's procedure[18] were unsuccessful.

As a result, *N*-acetylthiazolidinethione **9** was synthesized in a manner similar to oxazolidinethione **4**, with the exception that imine **7** was accessed from chloroacetaldehyde rather than from (4-methoxybenzyloxy)-acetaldehyde. Because the Grignard addition of mesitylmagnesium bromide provided a single diastereomer of the sulfinyl-protected amino chloride, this reaction could be quenched with HCl, neutralized, and directly treated with CS_2 and KOH to directly access thiazolidinethione **8**, shortening the reaction sequence. Subsequent exposure of thiazolidinethione **8** to acetyl chloride and NaH afforded (*S*)-*N*-acetylthiazolidinethione **9**.[19] It is important to note that the stereochemical results of the Grignard addition to imine **5** and imine **7** are opposite. The stereochemical outcome is dependent upon the coordinating ability of the substituent on the imine to magnesium.[12b]

Enolization of *N*-acetylthiazolidinethione **9** at −78 °C with $TiCl_4$ (1.1 equiv) and diisopropylethylamine (1.1 equiv) followed by addition of the aldehyde (1.0 equiv) resulted in highly diastereoselective aldol additions.[20] Aliphatic, aromatic, and α,*β*-unsaturated aldehydes were tolerated for this procedure (Table 2). Once again, the stereochemistry of the aldol adducts was determined by reductive cleavage of the adduct obtained in entry 4 to afford (*R*)-4-methyl-pentane-1,3-diol.[21] All diastereomers prepared to date have been completely separable by flash column chromatography

Table 2. Aldol Additions of Thiazolidinethione **9**



entry	aldehyde	yield (%)[a]	dr (**10**/**11**)[b]
1	PhCH=CHCHO	79	96:4
2	$(CH_3)_2CHCH_2CHO$	94	97:3
3	PrCHO	92	97:3
4	$(CH_3)_2CHCHO$	95	98:2
5	EtCHO	90	95:5
6	PhCHO	94	94:6

[a] Combined yield of diastereomers after purification. [b] Obtained by HPLC analysis of crude reaction mixtures.

resulting in major products of the reaction in >100:1 diastereomeric purity.

The observed stereochemistry in these acetate aldol additions can be explained by two possible models (Figure 1). The enolization conditions employed in these acetate aldol

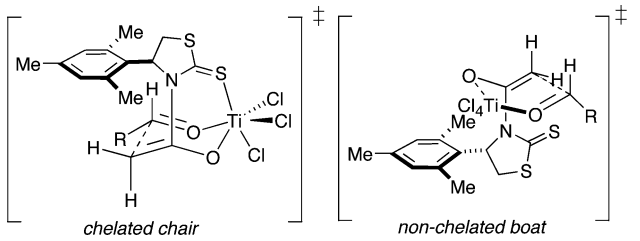


Figure 1. Possible transition states to account for acetate aldol stereochemistry.

additions are analogous to those employed in "non-Evans" *syn*-aldol additions for propionates. The propionate aldol additions are believed to proceed via a chelated transition state;[4a] therefore, diastereoselectivity would arise from the preference of the "R" group of the aldehyde to occupy a pseudoequatorial position to avoid a 1,3-diaxial interaction with both the auxiliary and one of the methyl groups on the mesityl group. Other possible transition states, such as a nonchelated boat, cannot be ruled out. Further studies are necessary to distinguish which transition state is operational in these reactions.

To explore the utility of this reaction in more stereochemically complex substrates, we next investigated the application

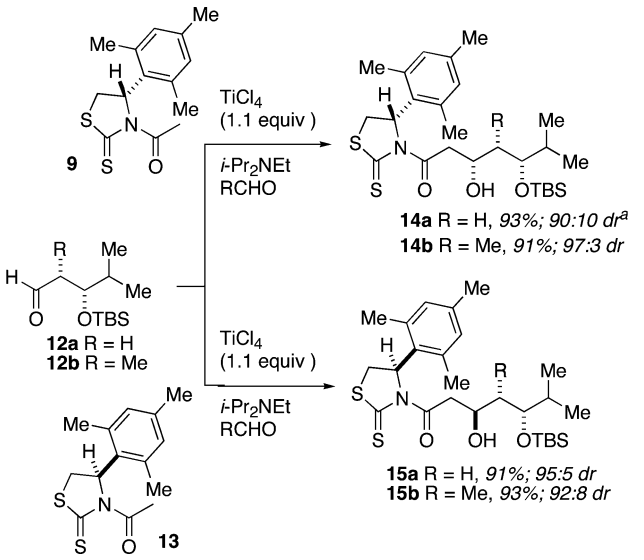
(18) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604.

(19) (*R*)-*N*-Acetylthiazolidinethione can be accessed from the same sequence of steps, starting from (*S*)-(−)-2-methyl-2-propane-sulfinamide.

(20) **Typical aldol procedure using *N*-acetylthiazolidinethione 9:** To a dry 25 mL round-bottom flask, under argon, was added *N*-acetylthiazolidinethione (0.307 g, 1.10 mmol) and 5.2 mL of CH_2Cl_2 (0.2 M). The solution was cooled to −78 °C, and titanium tetrachloride (neat, 0.12 mL, 1.10 mmol) was added and stirred for 5 min. Diisopropylethylamine (0.19 mL, 1.10 mmol) was added. The solution was stirred for 30 min at −78 °C, whereupon the freshly distilled aldehyde (neat, 1.0 mmol) was added dropwise. The mixture was stirred for 1 h at −78 °C, then quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hex to 20% EtOAc/Hex). Yields and diastereoselectivities are listed in Table 2.

(21) (*R*)-4-Methyl-pentane-1,3-diol: $[\alpha]_D = +9.30°$ ($c = 0.45$, $CHCl_3$). For the lit. value of (*R*)-4-methyl-pentane-1,3-diol, see: (a) ref 10c. (b) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A. *J. Org. Chem.* **1992**, *57*, 1412.

Scheme 3[a]



[a] Diastereomeric ratios obtained by HPLC analysis of crude reaction mixtures.

of thiazolidinethione **9** in double diastereoselective acetate aldol additions using nonracemic aldehydes.[22] Enantiopure aldehydes **12a** and **12b**[23] were subjected to acetate aldol additions with both enantiomers of the mesityl-substituted thiazolidinethione to provide aldol adducts **14a**, **14b**, **15a**, and **15b** in high yields with excellent diastereoselectivities (Scheme 3). The presence of an α-substituent on the aldehyde led to a drop in yield when the original enolization conditions[24] were applied. However, the yield increased significantly when a slight excess of the enolate was employed.[25]

In summary, we have described the concise synthesis of highly hindered oxazolidinethione and thiazolidinethione auxiliaries that achieve high levels of diastereoselectivity for acetate aldol additions employing aliphatic, aromatic, and α,β-unsaturated aldehydes. In addition, these auxiliaries also provide excellent double diastereoselection in the acetate aldol addition of nonracemic aldehydes. The application of this methodology toward the synthesis of a variety of polyketide-derived natural products is currently underway in our laboratory.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Double diastereoselective acetate aldol reactions using phenyldichloroboryl enolates of chiral *N*-acetylthiazolidinethione reagents have recently been examined by Sammakia: Zhang, Y.; Sammakia, T. *J. Org. Chem.* **2006**, *71*, 6262.

(23) Aldehyde **12a** was prepared via an acetate aldol addition. Aldehyde **12b** was prepared via a propionate aldol addition previously reported by our laboratory (ref **4a**). See Supporting Information for detailed procedure.

(24) Portions of 1.1 equiv of $TiCl_4$, 1.1 equiv of *i*-Pr_2NEt, and 1.1 equiv of thiazolidinethione **9**. See Supporting Information for detailed procedure.

(25) Portions of 1.5 equiv of $TiCl_4$, 1.5 equiv of *i*-Pr_2NEt, and 1.5 equiv of thiazolidinethione **9**. See Supporting Information for detailed procedure.