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Asymmetric Bromination-Aldolization of Chiral Acetate Titanium Enolate Derived from Thioimide. A General Approach to the Synthesis of Enantiopure α-Bromo-β-hydroxy Carboxylic Acids.

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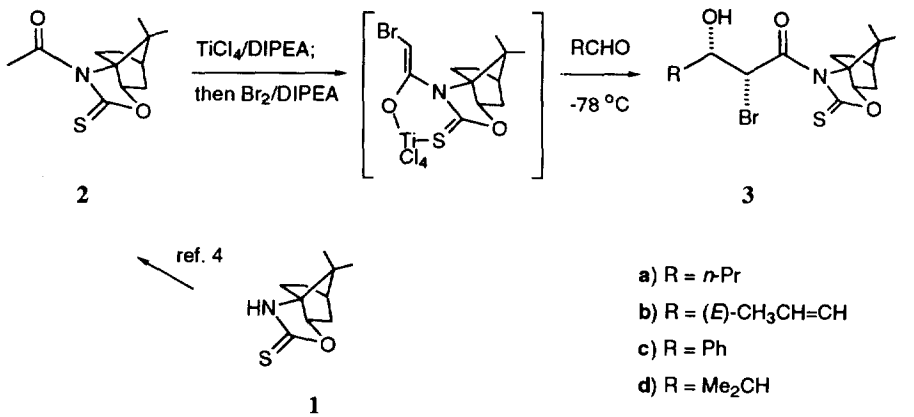
Abstract: Chiral acetate titanium enolate derived from thioimide efficiently effects one-step bromination-aldolization with excellent yields and exceptionally high levels of asymmetric induction in aldol additions. General base promoted oxazolidinethione deacylation provides direct access to chiral α-bromo-β-hydroxy acids.

Keywords: Aldol reactions; Asymmetric induction; Enolates; Halohydrins

Chiral α-bromo-β-hydroxy acids can serve as valuable building blocks for further structural elaboration as well as interesting substances in their own right. The development of chiral α-substituted acetate enolate synthons and their practical utility in aldol bond construction have been the subject of intensive investigation.[1,2,3] In light of recent reports, wherein the boron-mediated bromoacetate enolate aldolizations consistently proceeded to no more than 80% conversion[1a] and 52% yield,[1b] we wish to report that acetate titanium enolate derived from thioimide efficiently effects one-step bromination-aldolization with excellent yields and exceptionally high levels of asymmetric induction in aldol additions (Scheme 1).

Scheme 1



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We aimed at using previously reported camphor-based chiral *N*-acetyloxazolidinethione **2** as a starting

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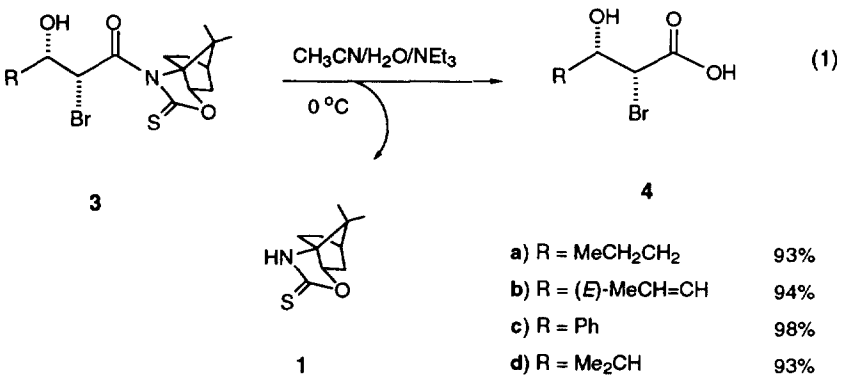
material and explored one-step enolate bromination-aldolization reactions (Scheme 1).[4] Enolization of **2** with $TiCl_4$[5,6] (1.6 equiv) and diisopropylethylamine (1.2 equiv) in CH_2Cl_2 (0 °C) followed by treatment with bromine (1 equiv) at -78 °C to give an intermediate adduct, which was isolated and characterized by NMR spectroscopy as the bromoacetate carboxthioimide.[7] Treatment of this intermediate, generated in situ, with an additional 1.2 equiv of diisopropylethylamine at -78 °C and subsequent aldolization of the resulting titanium bromoacetate enolate with representative aldehydes (1.5 equiv) at -78 °C led within 2 h the bromohydrin **3** in excellent yield (Scheme 1, Table). The crude aldol adduct showed only one set of signals in the 400-MHz ^1H NMR spectrum suggestive of exceptionally high levels of asymmetric induction. From the data in Table, it is clear that the reaction exhibits generality as well as extraordinary reactivity and stereoselection. We believe the enhanced electrophilicity of aldehyde carbonyl group, promoted by $TiCl_4$, is important to the observed generality and reactivity. The sense of asymmetric induction in this reaction is fully consistent with the observed stereochemical course of the previously reported propionate thioimide titanium enolate.[4a,8,9]

Table. Titanium Mediated Bromination-Aldolization Reactions of Acetate Thioimide **2**.

entry	electrophile	ratio[a]	yield[b] (%)	adduct
1	*n*-PrCHO	>99 : 1[c]	91	**3a**
2	(*E*)-MeCH=CHCHO	>99 : 1[c]	90	**3b**
3	PhCHO	>99 : 1[c]	94	**3c**
4	Me_2CHCHO	>99 : 1[c]	91	**3d**

[a] Ratios determined by 400-MHz ^1H NMR. [b] isolated yield. [c]The *syn* aldol **3** was the only detected product by ^1H NMR.

Can the initial thioimide aldol adduct be directed toward chiral α-bromo-β-hydroxy acids? Exposure of **3a** to $LiOH/H_2O_2$ produced bromohydrin acid **4a** but also a second product readily identified as epoxy acid by its spectroscopic properties. Since more basic reagent LiOH enhances epoxide formation, replacing LiOH by a base like triethylamine may serve as a general base catalyst for promoting deacylation but inhibiting internal S_N2 displacement of bromide. Indeed, in the reaction of **3a** with H_2O (6 equiv) in the presence of NEt_3 (3 equiv) in CH_2Cl_2 at 0 °C, epoxide formation was completely suppressed and **4a** was isolated in 93% yield with no apparent loss of stereochemistry (eq 1). Aldol adducts **3b**, **3c**, **3d** gave similar results.[10]



The data in the eq 1 document the finding that general base, e.g. NEt_3, promoted oxazolidinethione deacylation not only results in the suppression of epoxide formation, which is a major problem with more basic reagents such as LiOBn and LiOH,[1] but also affords bromohydrin in almost quantitative yield.

The preceding studies highlight the unexpected reactivity and stereoselection of bromoacetate titanium enolate aldolizations which offer a practical alternative to the use of other expensive metalloids such as boron to achieve excellent yield as well as exceptional stereocontrol. Synthetically, the successful control of oxazolidinethione deacylation expands the scope of asymmetric aldol addition method by providing direct access to chiral α-bromo-β-hydroxy acids. A general experimental procedure for bromination-aldolization is as follows.

To a solution of **2** (10 mmol) in 40 mL of CH_2Cl_2 cooled to 0 °C was added 16 mL (1 M in CH_2Cl_2, 16 mmol, 1.6 equiv) of $TiCl_4$. After stirring at 0 °C for 3 min, slow addition of diisopropylethylamine (1M in CH_2Cl_2, 12 mL, 12 mmol) and further stirring for 10 min at 0 °C, the reaction mixture was cooled to -78 °C. To the above reaction mixture was slowly added a solution of Br_2 (10 mmol) in 10 mL of CH_2Cl_2. After stirring at -78 °C for 10 min, a sceond equivalent of diisopropylethylamine (1 M in CH_2Cl_2, 12 mL, 12 mmol) was added and stirred for 10 min at -78 °C. To the above enolate solution was slowly added a solution of freshly distilled aldehyde (13 mmol) in 13 mL of CH_2Cl_2. The reaction mixture was stirred at -78 °C for 1.5 h and quenched with 40 mL of aqueous phosphate buffer (pH = 7). The aqueous layer was extracted with 60 mL of CH_2Cl_2. The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane, silica gel, 0-5 °C) afforded pure aldol **3**. **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 2.0 Hz, 1H, BrC*H*C=O), 4.54 (dd, J = 8.0, 4.0 Hz, 1H, C*H*O-C=S), 4.01 (m, 1H, CH_2CHOH), 2.76-1.20 (m, 12H, $CH_3CH_2CH_2$, O*H*, $CH_2CH_2CHCH_2$), 1.08 (s, 3H, CH_3-C-CH_3), 0.99 (s, 3H, CH_3-C-CH_3), 0.90 (m, 3H, CH_3CH_2); **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 4.4 Hz, 1H, BrC*H*C=O), 5.87 (dq, J = 15.6, 6.8 Hz, 1H, CH_3CH=CH), 5.56 (dd, J = 15.6, 6.8 Hz, 1H, CH_3CH=C*H*), 4.60 (dd, J = 6.8, 4.4 Hz, 1H, C=CHC*H*OH), 4.54 (dd, J = 8.0, 4.0 Hz, 1H, C*H*O-C=S), 2.73-1.18 (m, 11H, CH_3CH=C, O*H*, $CH_2CH_2CHCH_2$), 1.07 (s, 3H, CH_3-C-CH_3), 0.98 (s, 3H, CH_3-C-CH_3); **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.24 (m, 5H, C_6H_5CHOH), 7.00 (d, J = 4.4 Hz, 1H, BrC*H*C=O), 5.28 (d, J = 4.4 Hz, 1H, C_6H_5CHOH), 4.52 (dd, J = 8.0, 4.0 Hz, 1H, C*H*O-C=S), 2.73-1.20 (m, 8H, O*H*, $CH_2CH_2CHCH_2$), 1.02 (s, 3H, CH_3-C-CH_3), 0.90 (s, 3H, CH_3-C-CH_3); **3d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 2.0 Hz, 1H, BrC*H*C=O), 4.54 (dd, J = 8.2, 4.0 Hz, 1H, C*H*O-C=S), 3.68 (dd, J = 8.2, 2.0 Hz, 1H, C*H*OH), 2.68-1.20 (m, 9H, $CH(CH_3)_2$, O*H*, $CH_2CH_2CHCH_2$), 1.13 (s, 3H, CH_3-C-CH_3), 1.09 (d, J = 6.8 Hz, 3H, H_3CCHCH_3), 1.05 (s, 3H, CH_3-C-CH_3), 0.93 (d, J = 6.8 Hz, 3H, CH_3CHCH_3).

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9. The absolute stereochemical assignment of the bromohydrin **3d** is made via transesterification ($PhCH_2OH$), epoxide formation, and correlation of the resultant benzyl epoxy ester.[1b] On the basis of this analogue, the absolute configuration of the aldols **3a**, **3b**, and **3c** was similarly assigned.
10. *syn* acid **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (bs, 1 H, O*H*), 4.32 (d, *J* = 4.0 Hz, 1 H, CHC*H*C=O), 4.07 (m, 1 H, C*H*CHC=O), 1.67-1.37 (m, 4 H, CH_2CH_2), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2); $[\alpha]_D^{25}$ -89.7° (*c* 0.96, CH_2Cl_2); **4b**: δ 5.88 (dq, *J* = 15.2, 6.8 Hz, 1 H, CH_3HC=CH), 5.50 (dd, *J* = 15.2, 6.4 Hz, 1 H, CH_3HC=C*H*), 4.70 (bs, 1 H, O*H*), 4.47 (d, *J* = 6.4 Hz, 1 H, C*H*CHC=O), 4.28 (d, *J* = 6.4 Hz, 1 H, CHC*H*C=O), 1.75 (d, *J* = 6.8 Hz, 3 H, CH_3CH=C); $[\alpha]_D^{25}$ +71.2° (*c* 2.2, CH_2Cl_2); **4c**: δ 7.36 (bs, 5 H, C_6H_5), 5.39 (bs, 1 H, O*H*), 5.09 (d, *J* = 6.4 Hz, 1 H, HOC*H*CHBr), 4.47 (d, *J* = 6.4 Hz, 1 H, CHC*H*Br); $[\alpha]_D^{25}$ +13.8° (*c* 2.3, CH_2Cl_2); **4d**: δ 4.49 (d, *J* = 3.6 Hz, 1 H, CHC*H*C=O), 3.54 (dd, *J* = 6.8, 3.6 Hz, 1 H, C*H*CHC=O), 3.45 (bs, 2 H, O*H*, COO*H*), 1.85 (octet, *J* = 6.8 Hz, 1 H, $(CH_3)_2CH$CH), 1.04 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH$_3$), 0.92 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHCH_3); $[\alpha]_D^{25}$ +22.2° (*c* 1.2, CH_2Cl_2).