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Highly Enantioselective Routes to Darzens and Acetate Aldol Products from Achiral Aldehydes and *t*-Butyl Bromoacetate

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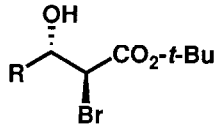
Summary: *New methodology is described for the enantioselective coupling of t-butyl bromoacetate with aldehydes to give anti-α-bromo β-hydroxy esters (**1**), useful precursors of chiral glycidic esters (**2**), acetate aldols (**3**), β-amino acid esters (**4**) and α-amino acid esters (**5**).*

We report herein the first highly enantioselective version of the Darzens reaction in which an achiral aldehyde and *t*-butyl bromoacetate can be converted to an intermediate chiral α-bromo β-hydroxy ester (**1**) as well as the chiral Darzens α,β-epoxy ester (**2**). These two products can serve as versatile precursors for many useful types of chiral compounds, for example acetate aldols (**3**), α-hydroxy β-amino esters (**4**), and α-amino β-hydroxy esters (**5**). The new enantioselective methodology has several merits: (1) enantioselectivities in the range 99 : 1 to 95 : 5, (2) diastereoselectivities in the range 99 : 1 to 95 : 5, (3) yields in the range 65-95%, (4) use of a readily available and easily recoverable chiral controller for the reaction, and (5) availability of either enantiomeric product with predictable chirality, depending on the use of either the (*R,R*) reagent **6** or the (*S,S*) enantiomer. Reagent **6** and the enantiomer have been shown previously to be highly effective in promoting propionate ester aldol reactions with aldehydes to give



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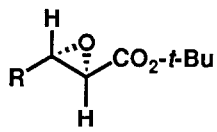

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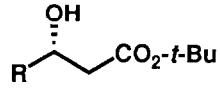

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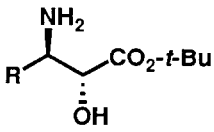

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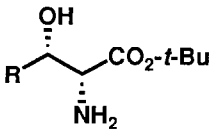

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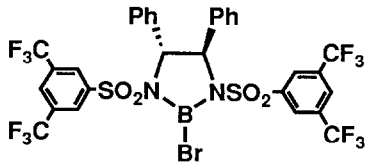

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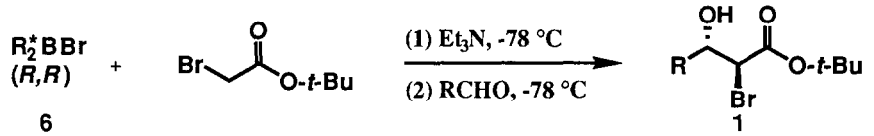
selectively any of the four possible aldol products.[1,2] Relevant prior work in this area includes the use of Evans aldol reactions of chiral 3-(chloroacetyl)-2-oxazolidinones with aldehydes,[3] Darzens reactions of α-halo ketones and aldehydes under phase transfer conditions with quaternary quinine salts to give α,β-

epoxy ketones of 8-15% ee,[4] and the use of boron or tin (II) enolates in diastereoselective, but not enantioselective, α-halo β-hydroxy ester synthesis.[5]

The reaction of *t*-butyl bromoacetate with the (*R,R*) bromoborane **6** (R^*_2BBr) and triethylamine in toluene or methylene chloride at -78 °C for 2 h produced the (*Z*)-boron enolate (OBR^*_2 and Br *trans*) stereoselectively.[1] Addition of an aldehyde (0.9 equiv) and reaction at -78 °C for 2 h followed by quenching with CH_3OH–H_2O at -78 °C, extractive isolation and silica gel purification afforded an anti α-bromo β-hydroxy ester **1** in excellent yield along with the bis-sulfonamide precursor of bromoborane **6** which could be recycled to **6**.[1] The results of such reactions with a series of four different types of aldehydes are summarized in Table I. The scope and effectiveness of this enantioselective and diastereoselective construction are evident.

Table I. Reactions of Bromoborane 6, *t*-Butyl Bromoacetate and Aldehydes.



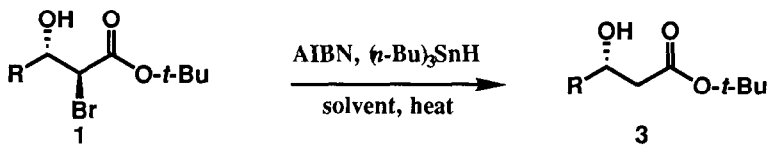
R of RCHO	Solvent[a]	Yield (%)	Anti/Syn[b]	% ee	$[\alpha]^{20}_D$ (c, $CHCl_3$)
C_6H_5	M	86	98/2	96	
C_6H_5	T	94	99/1	98	+97.5 (0.28)
(*E*)-C_6H_5CH=CH	T	96	99/1	98	-27.5 (0.42)
$C_6H_5CH_2CH_2$	M	70	92/8[c]	74	
$C_6H_5CH_2CH_2$	T	72	95/5[c]	91	-20.3 (0.53)
Cyclohexyl	T	65	98/2[c]	91[d]	-17.5 (0.65)

[a] M = CH_2Cl_2; T=1 : 2 toluene–hexane. [b] Anti/syn ratio and % ee were determined by HPLC analysis using a chiral Daicel OD column, except as noted. Absolute configuration was determined for the predominating enantiomer by optical rotation and/or comparison with an authentic sample. [c] Analysis by measurement of ^1H NMR Spectrum (500 MHz) [d] Analysis by ^1H NMR after conversion to the MTPA ester.[6]

Debromination of the α-bromo β-hydroxy esters with tri-*n*-butyltin hydride afforded good yields of the acetate aldol products **3** as summarized in Table II. Although the same enantiomer **3**[7] could also be obtained directly from **6**, *t*-butyl acetate, triethylamine and RCHO in CH_2Cl_2, the enantioselectivities for the direct acetate aldol reactions were in the range 80-85%, i.e. below that for the two-step synthesis via **1**. Thus, the synthesis of acetate aldols via **1** can be advantageous.[8]

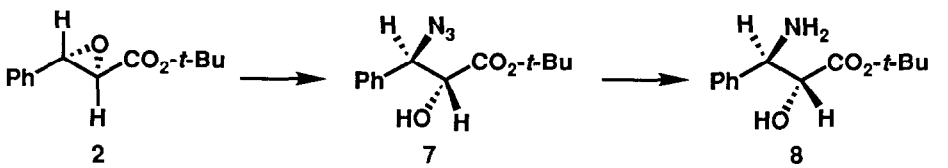
The transformation of the α-bromo β-hydroxy esters **1** into α,β-epoxy esters **2** (glycidic or Darzens esters) is readily effected by reaction with 1 equiv of KO*t*-Bu in *t*-BuOH. Thus for **1**, R=C_6H_5, exposure to 1 equiv of KO*t*-Bu in *t*-BuOH at 20 °C for 2 h provided after isolation and purification α,β-epoxy ester **2**, R=C_6H_5, $[\alpha]^{23}_D$ - 140° (c=0.85, $CHCl_3$), in 82% yield. This levorotatory α,β-epoxy ester was synthesized independently for comparison by the sequence: (1) Katsuki-Sharpless oxidation with (*R,R*)-(+)-diethyl

Table II. Reduction of α-Bromo β-Hydroxy Esters



R	Solvent	*n*-Bu_3SnH, eq.	AIBN, eq.	Time at Reflux	Yield (%)
C_6H_5	benzene	2.0	0.5	1 h	74
C_6H_5	toluene	5.0	0.2	40 min	82
(*E*)-C_6H_5CH=CH	benzene	2.0	0.15	15 h	62
(*E*)-C_6H_5CH=CH	toluene	5.0	0.2	30 min	96
$C_6H_5CH_2CH_2$	toluene	5.0	0.2	30 min	87
Cyclohexyl	toluene	5.0	0.2	30 min	81

tartrate, Ti(O*i*-Pr)$_4$ and *t*-BuOOH in CH_2Cl_2, (2) oxidation with CrO_3-pyridine-Ac_2O-*t*-BuOH[9] which yielded **2**, R=C_6H_5, $[\alpha]_D^{23}$ - 111° (c=1.8, $CHCl_3$). Glycidic esters are of special value as intermediates for the synthesis of therapeutically interesting β–amino α-hydroxy acids. To demonstrate this approach for chiral **2**, R=C_6H_5, this substance was treated with sodium azide in 4 : 1 *t*-BuOH–H_2O at 50 °C for 24 h to afford cleanly the β-azido α-hydroxy ester **7** in 75%, which underwent reduction (1 atm H_2, Pd–C, THF, 20 °C, 20 h) to form the β-amino α-hydroxy ester **8** (88% isolated yield).



Protection of the β-hydroxy group in **1** as the *t*-butyldimethylsilyl ether (*t*-butyldimethylsilyl triflate, 2,6-lutidine in CH_2Cl_2 at 0 °C for 3 h, 81%) and reaction with 5 equiv of sodium azide in dimethylformamide (0.5 M concentration of NaN_3) at 70 °C for 20 h afforded 89% of the α-azido β-silyloxy ester **9**.[10] Reduction of **9** (1 atm H_2, Pd–C, THF, 20 °C, 36 h) afforded the α-amino acid derivative **10**.

The new methodology reported herein permits ready access to many useful chiral hydroxy ester derivatives with good enantiomeric purity. The following procedure illustrates the key enantioselective step.

***t*-Butyl (2*S*,3*S*)-(+)-2-Bromo-3-hydroxy-3-phenylpropionate 1, R=C_6H_5.** The (*R*,*R*)-(+)-Bis-3,5-di(trifluoromethyl)benzenesulfonamide **6**[1] (229.2 mg, 0.3 mmol) was placed in a flame dried 50 mL round-bottomed flask equipped with magnetic stirring bar and sealed with a rubber septum. The flask was evacuated and flushed with argon three times. Freshly distilled dichloromethane (3 mL) was added and the homogeneous solution was treated with BBr_3 (0.5 M solution in dichloromethane, 1.2 mL, 0.6 mmol). The solution was warmed to 45 °C, kept at 45 °C for 3 h with stirring, and concentrated under vacuum (ca. 1 mm Hg) by using a metal tube inserted through the septum. Dryness of the vacuum line was maintained with a drying tube containing NaOH pellets and $CaSO_4$ to prevent possible hydrolysis of bromoborane **6**. Dry dichloromethane (1 mL) was added and evaporated under vacuum as above. Freshly distilled toluene (10 mL) was added and the resulting mixture was warmed to effect complete solution, and then diluted with freshly distilled hexane (20 mL). The homogeneous solution of bromoborane **6** was cooled to -78 °C and then treated with *t*-butyl bromoacetate (58.5 mg, 48.4 mL, 0.3 mmol), and stirred for 1 min. Triethylamine (33.4 mg, 46.0 mL, 0.33 mmol) was added, the resulting solution was stirred for 2 h at -78 °C. Benzaldehyde (28.7 mg, 27.4 mL, 0.27 mmol) in toluene (0.5 mL) was dropped in over 5 min. The reaction was allowed to proceed for 2 h at -78 °C and then quenched by addition of methanol (0.5 mL) and water (5 mL) at -78 °C. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. Final purification of the crude product by silica gel chromatography (13% ethyl acetate in hexane) gave the bromo alcohol **1** as a colorless liquid (78.1 mg, 96% yield); $[\alpha]_D^{20}$ + 97.5° (c=0.28, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.46(s, 9H), 3.41(d, *J*=5.7Hz, 1H), 4.29(d, *J*=7.6Hz, 1H), 5.03(dd, *J*=7.6, 5.7Hz, 1H), 7.31-7.42(m, 5H); IR (neat, cm^{-1}) 3453(br.), 1733; TLC R*f* = 0.43 (17% ethyl acetate in hexane).[11]

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7. The absolute configurations of **3**, R=C_6H_5, R=*i*-Pr and R=cyclohexyl, were determined by reduction with $LiAlH_4$ and measurement of optical rotation. Found for the (*R*)-diol from **3**, R=C_6H_5: $[\alpha]_D^{23}$ + 63° (c=1, $CHCl_3$); for the (*R*)-diol from **3**, R=cyclohexyl: $[\alpha]_D^{23}$ + 8.0° (c=0.6, $CHCl_3$); see, Kim, B.; Ph.D. dissertation M.I.T., Feb. 1988. Found for the (*R*)-diol from **3**, R=*i*-Pr: $[\alpha]_D^{23}$ + 6.67° (c=1.3, $CHCl_3$); see Rossiter, B. E.; Sharpless, K. B.; *J. Org. Chem.* **1984**, *49*, 3707-3711.
8. See also, Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031-5034; Braun, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24-37.
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10. A small amount (< 10%) of the α-epimeric azide diastereomer was formed in this process via α-deprotonation–reprotonation, a more serious side reaction under other conditions.

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