Pergamon

*Tetrahedron Letters*, Vol. 37, No. 21, pp. 3747-3750, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00637-5

# Boron Aldol Reaction of α-Halosubstituted Thioacetates with Silyl Imines: A Highly Enantio- and Diastereoselective Synthesis of Aziridines

**Cesare Gennari* and Gilles Pain**

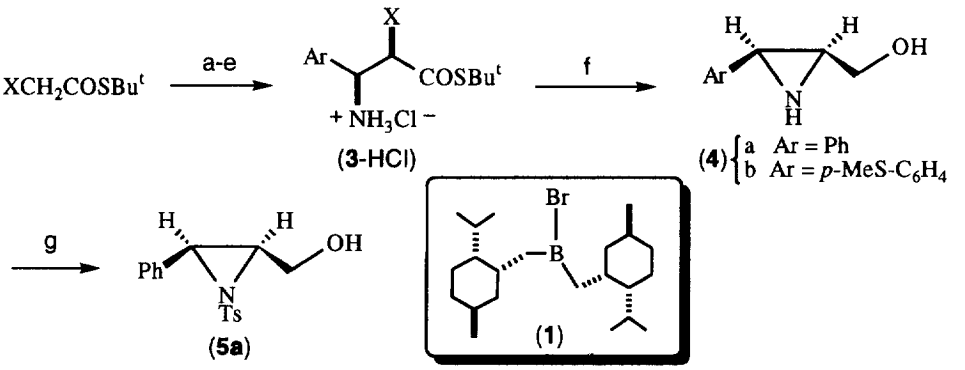
Dip. di Chimica Organica e Industriale, Universita' di Milano, Centro CNR (Sost.Org.Nat.), via Venezian 21, 20133 Milano, Italy

***Abstract***: Boron enolates derived from *tert*-butyl α-halothioacetate and bearing menthone-derived chiral ligands react with imines with excellent diastero- and enantiocontrol to give *syn* α-halo-β-aminothioesters, which can be converted to the corresponding aziridines by simple ring closure during LAH reduction. A key precursor of antibiotics (+)-thiamphenicol and (-)-florfenicol was synthesized.


β-Amino acids, although less abundant than their α-counterparts, are components of natural peptides,[1a] and show interesting biological properties. They also display a wide spectrum of synthetic applications, including the preparation of modified peptides[1b] and β-lactam antibiotics.[1c] Numerous methods for the synthesis of β-amino acids exist, and have been recently reviewed:[1d-g] one of the most useful involves the reaction of imines with enolates.[1f] In order to make this process stereoselective, chiral auxiliaries have been attached either to the enolate[2] or to the imine,[3] or both.[4] In alternative, the use of achiral imines and boron enolates bearing chiral boron ligands was recently described.[5] The reaction of α-haloesters with chiral imines leads to the synthesis of chiral aziridines (Darzens type).[6]

Here we report on the addition of boron enolates derived from *tert*-butyl α-halothioacetates (X = Cl, Br) and the chiral boron reagent **1** [derived from (+)-menthone],[7a-e,8] to achiral *N*-trimethylsilylimines **2**[9,10] (Scheme 1). α-Halo-β-amino thioesters were isolated in 77-89% yield as hydrochloride salts (**3**-HCl). The diastereoselectivity of the reaction was checked on the *N*-benzoyl derivatives (**6**, Scheme 2, *vide infra*) and on the Mosher derivatives, and shown to be high (*syn: anti* 92:8 - ≥99:1). The enantiomeric ratios of the major *syn* products were determined by $^1$H-NMR analysis of the Mosher derivatives,[11] and shown to be 97:3 - ≥99.5:0.5 (Table 1). Non protected chiral aziridine alcohols (**4**) were easily obtained (86-91%) by simple reduction with $LiAlH_4$ of the α-halo-β-amino thioesters **3**. The *syn* relationship of the aldol adducts **3** was thus proved by the formation of *cis* aziridine alcohols **4** (Scheme 1). The *cis* aziridine stereochemistry was demonstrated by the $^1$H-NMR coupling constants (*J cis* = 6.4-6.6 Hz; average literature values for *J trans* = 2.5-3.0 Hz)[12a,b] and by correlation with the known compound **4b**.[6b] (1H)-(2*S*,3*S*)-(+)-3-[(4-methylthio)phenyl] aziridine-2-methanol (**4b**) is a key intermediate for the synthesis of the broad spectrum, antibacterial, synthetic antibiotics (+)-thiamphenicol and (-)-florfenicol.[6b]

The synthesis of chiral non-racemic aziridines continues to be a major area of interest in organic chemistry: aziridines are useful building blocks for the preparation of amino alcohols and amino acids, and many ring-opening reactions have been described using a range of nucleophiles.[12]



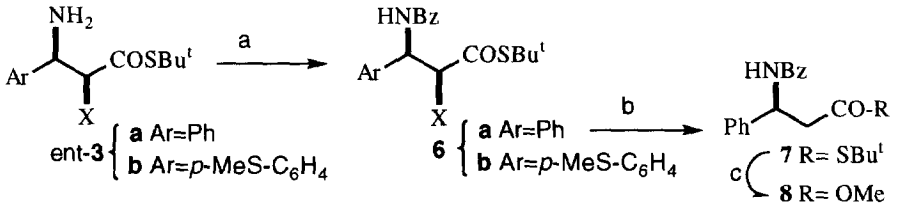

Scheme 1. Addition of the chiral boron enolates derived from α-halothioacetates to silylimines: a) L**$_2$BBr (**1**) derived from (+)-menthone (see ref. 7,8), $Et_3N$, $CH_2Cl_2$, $Et_2O$, 0°C, 1.5 h; b) ArCH=NSiMe$_3$ (**2**), -78°C to -5°C; c) pH 7 phosphate buffer quenching, $CH_2Cl_2$ extraction, evaporation; d) $Et_2O$, 1 N aqueous HCl, RT; evaporation; e) solid washed with $Et_2O$ (77-89% yield over steps a-e); f) from **3**: $LiAlH_4$, THF, 0°C (86-91%); g) from **4a**: TsCl, $CHCl_3$, $Et_3N$, -40°C to 0°C (89%). $[\alpha]_D^{25}$ (c 0.71, $CHCl_3$) of **4b** [derived from **3b** (X=Br)] = + 95.7°. Lit. (ref. 6b) (c 0.70, $CHCl_3$) = + 96.8°. $[\alpha]_D^{25}$ (c 0.90, $CHCl_3$) of **5a** [derived from **3a** (X=Br)] = + 123.1°. Lit. (ref. 12d) for ent-**5a** (c 1.32, $CHCl_3$) = - 126.9°.

Table 1

| X | Ar | Compound | *Syn: anti* ratio | % e.e. (*syn* diast.) | % Yield |
|---|---|---|---|---|---|
| Br | Ph- | **3a** | ≥ 99: 1 | 97 | 80 |
| Br | *p*-MeS-$C_6H_4$- | **3b** | ≥ 99: 1 | ≥ 99 | 77 |
| Cl | Ph- | **3a** | 92: 8 | 94 | 89 |
| Cl | *p*-MeS-$C_6H_4$- | **3b** | 94: 6 | 95.7 | 85 |

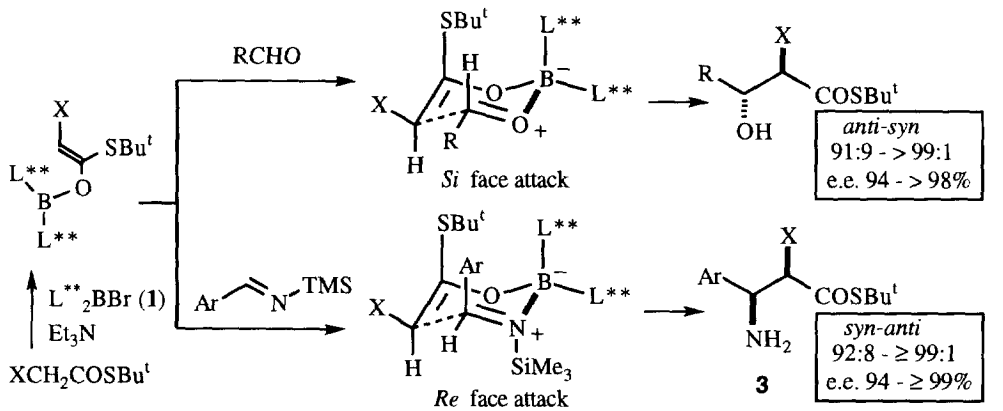
Aziridine **4a** was transformed into the corresponding *cis N*-tosyl-3-phenyl-2-aziridinemethanol **5a** (89%).[12c,d] Chiral *N*-tosylaziridinemethanols are key intermediates for the synthesis of various classes of compounds, as they easily undergo nucleophilic $S_N2$-type ring-opening and aza-Payne rearrangement due to the presence of the activating *p*-toluensulfonyl group.[12c,d]

The imine π-face selectivity was further proved by determining the absolute configuration at the C-N stereocenter by chemical correlation with the known compound **8** (Scheme 2). α-Halo-β-amino thioesters ent-**3** [obtained using L*$_2$BBr (ent-**1**) derived from (-)-menthone][7,8] were benzoylated using benzoic acid and DCC to give **6** (85%). The *syn:anti* ratios were checked on N-benzoyl derivatives **6** via $^1$H-NMR spectroscopy. Reductive elimination of the halogen atom of **6a** using Zn/$NH_4Cl$ in methanol gave **7** (60-75%), which was transformed into methyl ester **8** by reaction with $Hg(NO_3)_2$ in methanol (82%). The $[\alpha]_D$ value of **8** was in good agreement with that reported in the literature.[3e] The optical purity of methylester **8** [O.P. = 97.8% for **8** derived from ent-**3a** (X = Br); 90% for **8** derived from ent-**3a** (X = Cl)] reflects the higher stereoselectivity of the reaction using the α-bromoacetate compared to the α-chloroacetate. It is also worthnoting that, in the case of **8** derived from ent-**3a** (X = Cl), this value was obtained starting from a *syn:anti* mixture (*syn:anti* 92:8) without removing the minor *anti* diasteroisomer. The NMR analysis of the Mosher derivatives of ent-**3a** (X = Cl) shows that while the major *syn* isomer is 94% enantiomerically pure, the minor *anti* isomer is more or less racemic.




Scheme 2. Chemical correlation of α-halo-β-amino thioesters ent-**3** [obtained using $L^*_2BBr$ (ent-**1**) derived from (-)-menthone, see ref. 7,8]: a) $PhCO_2H$, DCC, $CH_2Cl_2$ (85%); b) Zn, $NH_4Cl$, MeOH (60% X=Cl; 75% X=Br); c) $Hg(NO_3)_2$, MeOH (82%). $[\alpha]_D^{25}$ (c 0.63, $CHCl_3$) of **8** [derived from ent-**3a** (X=Br)] = + 20.0°. Lit. (ref. 3e) for ent-**8** (c 1.12, $CHCl_3$) = - 20.45°.

We have recently reported that the enolates derived from α-halothioacetates (X = Cl, Br) and the chiral boron reagent **1** or ent-**1** react with aldehydes to give α-halo-β-hydroxy derivatives with high diastereo- (*anti:syn* 91:9 - >99:1) and enantiocontrol (e.e. = 94 - >98%).[7d] It is interesting to note that the stereochemistry of the imine (*trans*) determines the *syn* stereochemical relationship in the aldol product **3**. In fact, the absolute configuration of **3** is consistent with a chair transition structure featuring preferential attack on the imine *Re* face. We can also note that in the aldehyde case, the R group can adopt an equatorial position (aldehyde *Si* face attack) which eventually leads to the *anti* relationship between the hydroxy and the halogen groups (Scheme 3). In contrast with the model suggested by Corey,[5a] and in agreement with the models proposed by Cozzi and Cinquini[5b] and Yamamoto,[5c] we believe that the transition state involves an (*E*) configurated imine, that does not isomerize to (*Z*) during the aldol reaction. Boat transition states leading to the minor *anti* diastereomer cannot be ruled out, as suggested by MO transition state calculations of the addition of lithium enolates to silyl imines.[10a] *Ab initio* MO calculations (3-21G basis set) featuring the addition of the $BH_2$ enol borinate derived from acetaldehyde to formaldehyde-imine have recently shown that two competing cyclic transition structures are important: the chair and the boat.[13,14]




Scheme 3. Transition state models for the addition reactions to aldehydes and imines. $L^{**}_2BBr$ (**1**) derived from (+)-menthone.

***Acknowledgements.*** We thank Mr. Angel Gonzalez Solana (on leave from the University of Barcelona, Catalonia) for running some of the reactions in this project. We thank the Commission of the European Union (HCM Network Grant: ERB CHR XCT 930141) for financial support, for a research fellowship (to G.P.) and for sponsoring a research stage (to Angel Gonzalez Solana).

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(*Received in UK* 19 *March* 1996; *accepted* 3 *April* 1996)