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SELECTIVE SYNTHESIS OF OPTICALLY ACTIVE 3-HALOAZETIDIN-2-ONES OR AZIRIDINES BY THE CONDENSATION OF VARIOUS METAL ENOLATES OF α-HALOACETATE WITH A CHIRAL IMINE

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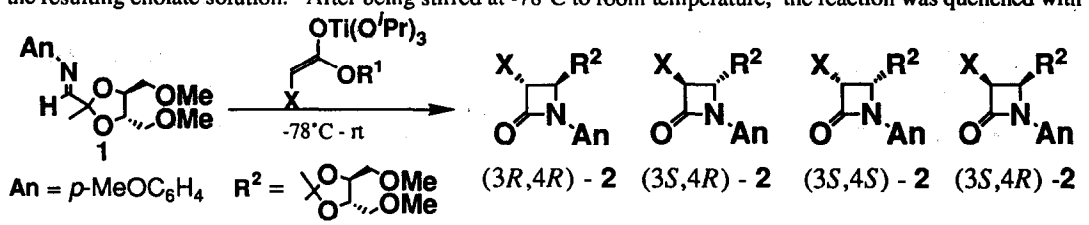
SUMMARY: Reaction products and their diastereofacial selectivity in the condensation of the ester enolates of α-haloacetate with a chiral imine possessing 1,3-dioxolane ring derived from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol as a chiral auxiliary can be fully controlled by the metal enolate used; *i.e.*, (3*R*,4*R*)-3-haloazetidine-2-one is obtained stereoselectively by the use of the triisopropoxytitanium enolates, while condensation with the lithium or zinc enolates provides (2*R*,3*S*)- or (2*S*,3*R*)-aziridine, respectively.

Recently significant attentions have been focused on the chemistry of β-lactamase inhibitors such as 6-halopenicillanic acids.[1] For the stereoselective synthesis of such a class of compounds 3-haloazetidin-2-one has been also employed as a synthetic intermediate,[2] and among them 3-chloroazetidin-2-ones appear to be employable for the preparation of β-lactamase inhibitors as well as β-lactam antibiotic, carpetimycin. Stereoselective synthesis of 3-fluoroazetidin-2-one is currently of great interest,[3] because many of fluorinated analogues cause a drastic change in biological activity. Although 3-haloazetidin-2-ones have been generally prepared by the ketene-imine cycloaddition method,[3c,4] only a single report deals with the preparation by the enolate-imine condensation reaction[5] leading to racemic 3-alkyl-3-fluoroazetidin-2-one.[3c] In addition, under comparable conditions aziridine has been reported to be obtained by the α-haloester enolate-silylimine condensation.[6] We have found that the reaction mode leading to either 3-haloazetidin-2-ones or aziridines could be controlled by selecting an appropriate metal enolate species derived from α-haloester enolate and would like to describe herein the first synthesis of optically active (3*R*,4*R*)-3-chloro- and 3-fluoroazetidin-2-ones or aziridines by the α-haloester enolates-imine condensation reaction utilizing characteristic features of the enolate metal species.

In a typical procedure a solution of *t*-butyl chloroacetate in THF was added dropwise to a solution of LDA in THF with stirring at -78°C for 15 min, and then a solution of $ClTi(O^iPr)_3$[7] in hexane was added at -78°C in 15 min. Then a solution of (4*S*,5*S*)-4,5-dimethoxymethyl-2-(*N*-*p*-methoxyphenyl)iminomethyl-2-methyl-1,3-dioxolane **1**, prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in 3 steps,[8] in THF was added dropwise to the resulting enolate solution. After being stirred at -78°C to room temperature, the reaction was quenched with



(3*R*,4*R*) - **2** (3*S*,4*R*) - **2** (3*S*,4*S*) - **2** (3*S*,4*R*) -**2**

Table 1. Reaction of the Triisopropoxytitanium Enolates of α-Haloesters to Chiral Imine 1[a)]

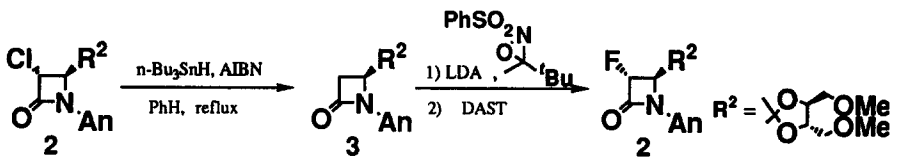
Entry	X	R^1	Enolate / eq	Solvent	Yield / %[b)]	(3*R*,4*R*):(3*S*,4*R*):(3*S*,4*S*):(3*R*,4*S*)[c)]
1	Cl	Et	6	THF	91	89 : 1 : 10 : 0
2	Cl	^{t}Bu	6	THF	41	100 : 0 : 0 : 0
3	Cl	^{t}Bu	10	THF	74	100 : 0 : 0 : 0
4	Cl	^{t}Bu	6	DME	77	100 : 0 : 0 : 0
5	F	^{t}Bu	6	THF	41	100 : 0 : 0 : 0
6	F	^{t}Bu	10	THF	65	100 : 0 : 0 : 0

a) All reactions were performed on 0.3 mmol scale at -78°C - rt. b) Isolated yields. c) The ratios were determined by capillary GLC (SE-30, 50m).

sat aq NH_4Cl. Purification by TLC on buffered silica gel[9] gave the directly cyclized 3-chloroazetidin-2-one **2** (X = Cl).[10] Under the same conditions, 3-fluoroazetidin-2-one **2** (X = F)[11] was also obtained by the condensation of the enolate of *t*-butyl fluoroacetate with the chiral imine **1**.

As shown in Table 1, no complete diastereoselectivity was observed in the condensation of the triisopropoxytitanium enolate of ethyl chloroacetate with the chiral imine **1**, whereas the use of *t*-butyl haloacetate accomplished the formation of (3*R*,4*R*)-isomers exclusively. In strong contrast to the previous report,[6] the present triisopropoxytitanium enolate effected the formation of 3-haloazetidin-2-one in a stereospecific manner. This unprecedented selectivity is quite noteworthy and can be explained reasonably in terms of the relatively weak ionic but moderate Lewis acidic character of the intermediary titanium amide. Accordingly, preferential attack of titanium amide to the ester part was smoothly achieved chemoselectively.

The relative stereochemistry at C_3 and C_4 of 3-haloazetidin-2-one was determined by the comparison of the coupling constant between C_3 and C_4 protons in ^{1}H NMR with the reported ones,[4a] which showed the *trans* form of J = 1.98 Hz for the chloro, J = 1.32 Hz for the fluoro, and the *cis* form of J = 5.45 Hz for the chloro derivative. The absolute stereochemistry of 3-chloroazetidin-2-one **2** (X = Cl) was determined to be (3*R*,4*R*)-form by the reductive dechlorination to the known azetidin-2-one **3**.[8] The absolute stereochemistry of 3-fluoroazetidin-2-one **2** (X = F) was determined to be (3*R*,4*R*)-form by comparison with the authentic sample prepared via hydroxylation[13] of the known azetidin-2-one **3** with the oxaziridine followed by fluorination with DAST.[3b]



On the other hand, dramatic change of the product was observed when the lithium and zinc enolates were used. No formation of azetidin-2-one could be observed, and instead, aziridine **4** was obtained in a stereodivergent fashion by the condensation of the lithium or zinc enolate of *t*-butyl chloroacetate with the chiral

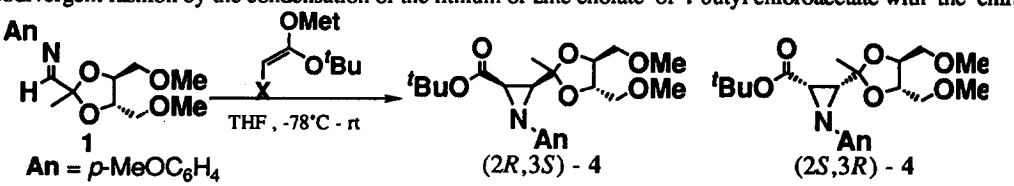


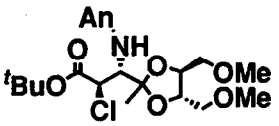
Table 2. Reaction of the Lithium or Zinc Enolates of α-Haloesters to Chiral Imine 1[a)]

Entry	X	Met	Enolate / eq	Yield / %[b)]	(2*R*,3*S*) : (2*S*,3*R*)[d)]
1	Cl	Li	3	44	91 : 9
2[c)]	Cl	Li	3	35	100 : 0
3	Br	Li	10	49	100 : 0
4	Cl	Zn	3	59	0 : 100
5	Br	Zn	6	9	0 : 100

a) All reactions were performed on 0.3 mmol scale at -78°C - rt. b) Isolated yields. c) The reaction temperature was -78°C - -50°C. d) The ratios were determined by HPLC.

imine **1**. The (2*R*,3*S*)-aziridine was obtained as a sole product when the lithium enolate was used, whereas the chlorozinc enolate effected the formation of (2*R*,3*S*)-isomer exclusively. The relatively strong ionic character of lithium or chlorozinc amide may be responsible for the selective substitution of chlorine rather than the cyclization to azetidin-2-one, and the complete reversal of the diastereoselectivity can be understood by considering the different coordination ability of the lithium and zinc metals.[14] Although the aziridine was formed in low yield in the reaction of the lithium enolate of *t*-butyl bromoacetate, an improved yield was attained by the use of 10 equivalents of the enolate, where the low yield is attributable to the self-condensation during the preparation of the metal enolate.

The relative stereochemistry of C_2 and C_3 of the aziridine derived from the lithium enolate was determined from the coupling constant between C_2 and C_3 protons, which showed *cis* coupling of J = 6.93 Hz.[15] The absolute stereochemistry was determined to be (2*R*,3*S*)-form by comparison with the authentic sample prepared via cyclization of the adduct **5**, which was obtained by the condensation of the titanium enolate of *t*-butyl chloroacetate with the chiral imine **1** at -78 - -60°C, whereas the same condensation at -78 °C - rt gave (3*R*,4*R*)-**2** to establish the structure of the intermediate **5**.



5

LDA / THF → (2R,3S) - **4**

In conclusion, the reaction mode leading to either 3-haloazetidin-2-ones or aziridines can be controlled by simply selecting the metal enolate species derived from *t*-butyl haloacetates in the condensation with a chiral imine **1**. Furthermore, diastereofacial discrimination was recognized in those azetidin-2-one and aziridine formations. In particular, formation of either diastereomer of *cis* form with respect to the aziridine ring was accomplished by selecting the lithium or chlorozinc enolate. Thus the present method provides a useful entry into the preparation of optically active 3-haloazetidin-2-ones and aziridines from a single starting material by the choice of the appropriate metals of ester enolates.

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9. The buffered silica gel was prepared by suspending 125g of silica gel (Wakogel B-5F) in 260 ml of phosphate buffer solution (pH 7.0) for 3 hr.
10. ^{1}H NMR (270 MHz, CDCl3) δ 1.46 (s, 3H), 3.31 (s, 3H), 3.32 (s, 3H), 3.36-3.46 (m, 4H), 3.79 (s, 3H), 4.06-4.13 (m, 2H), 4.27 (d, 1H, *J* = 1.98 Hz), 4.73 (d, 1H, *J* = 1.98 Hz), 6.86 (d, 2H, *J* = 9.08 Hz), and 7.51 (d, 2H, *J* = 9.08 Hz); IR (neat) 2980, 2945, 1775, 1640, 1519, 1450, 1400, 1300, 1250, 1150, 1100, and 950 cm^{-1}.
11. ^{1}H NMR (270 MHz, CDCl3) δ 1.47 (s, 3H), 3.32 (s, 3H), 3.35 (s, 3H), 3.36-3.43 (m, 5H), 3.80 (s, 3H), 4.06-4.10 (m, 1H), 4.36 (dd, 1H, *J* = 1.32, 12.5 Hz), 5.42 (dd, 1H, *J* = 1.32, 55.6 Hz), 6.87 (d, 2H, *J* = 8.91 Hz), and 7.52 (d, 2H, *J* = 8.91 Hz); IR (neat) 2905, 1780, 1630, 1535, 1475, 1400, 1318, 1260, 1100, 850, and 765 cm^{-1}.
12. ^{1}H NMR (270 MHz, CDCl3) δ 1.51 (s, 9H), 1.57 (s, 3H), 2.44 (d, 1H, *J* = 6.93 Hz), 2.62 (d, 1H, *J* = 6.93 Hz), 3.32 (s, 3H), 3.41 (s, 3H), 3.50-3.58 (m, 4H), 3.76 (s, 3H), 3.88-3.91 (m, 1H), 4.08-4.28 (m, 1H), 6.79 (d, 2H, *J* = 8.91 Hz), and 6.97 (d, 2H, *J* = 8.91 Hz); IR (neat) 2980, 2930, 1750, 1640, 1515, 1460, 1370, 1240, 1160, 1100, 950, and 840 cm^{-1}.
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