Stereoselective Synthesis of δ-Amino-β′-Hydroxy-β,γ-Unsaturated Esters by the Samarium(II) Iodide-mediated Aldol Reaction of Aldehydes with γ,δ-Aziridiny-α,β-Unsaturated Esters

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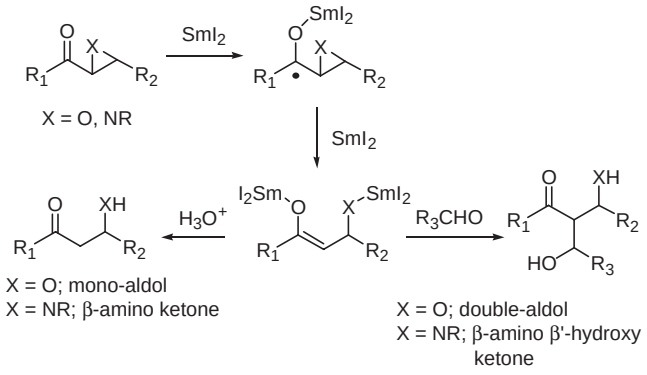
δ-Amino-β′-hydroxy-β,γ-unsaturated esters were stereoselectively synthesized by the aldol reaction of aldehydes with samarium enolates generated by aziridine-fragmentation of γ,δ-aziridinyl-α,β-unsaturated esters using two moles of samarium(II) iodide.

Samarium(II) iodide (SmI_2) is known as a powerful one-electron reducing agent[1] and is widely used in organic synthesis.[2] As shown in Scheme 1, it was reported that the reduction of oxiranyl ketones or aziridinyl ketones with SmI_2 in the presence of protic compounds such as methanol afforded mono-aldols or β-amino ketones through intermediate samarium enolates.[3] On the basis of these results, preparation of 3-hydroxy-2-(1-hydroxyalkyl)alkyl ketones (double-aldols) or 3-amino-2-(1-hydroxyalkyl)alkyl ketones (β-amino-β′-hydroxy ketones) by SmI_2-mediated aldol reaction of aldehydes with oxiranyl ketones or aziridinyl ketones was studied,[4,5] which were then successfully applied to synthesis of taxane skeleton.[6]

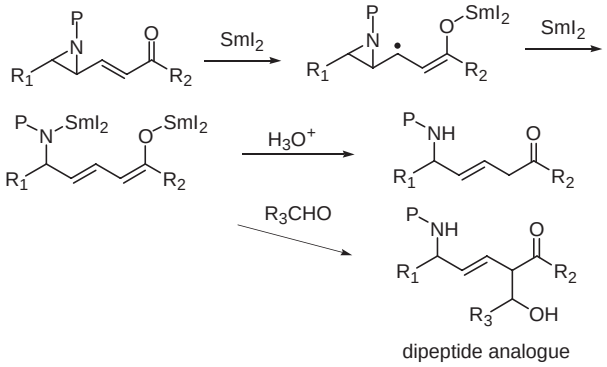
Next, the use of γ,δ-aziridinyl-α,β-unsaturated esters instead of the above mentioned oxiranyl ketones or aziridinyl ketones was studied in order to explore new possibilities for their application to synthetic chemistry. Aldol adducts thus formed here were considered to be δ-amino-β′-hydroxy-β,γ-unsaturated esters (Scheme 2).

The replacement of amide bond in bioactive peptides with a *trans*-double bond has long been a topic of interests in biological, theoretical, and synthetic areas. δ-Amino-β′-hydroxy-β,γ-unsaturated esters have been considered as important analogues of dipeptide and are expected to be used for building blocks to synthesize various biologically important polypeptides. In this communication, we would like to describe a new and efficient method for the stereoselective synthesis of δ-amino-β′-hydroxy-β,γ-unsaturated esters.

In the first place, SmI_2-mediated aldol reaction of (2′*R*,2*E*)-



Scheme 1.



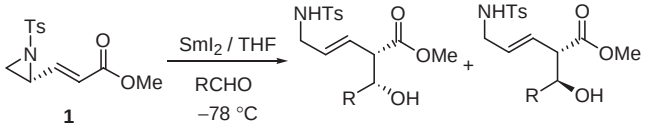
Scheme 2.

3-(1′-tosylaziridin-2′-yl)acrylic methyl ester (**1**)[7] with several aldehydes was examined (Table 1). Reaction of **1** with benzaldehyde gave the corresponding δ-amino-β′-hydroxy-β,γ-unsaturated ester (**1a**) (27/73 mixture of *syn* and *anti* isomers)[8] in good yield along with a small amount of δ-*N*-tosylamino-β,γ-unsaturated methyl ester (Entry 1). The yield of **1a** slightly decreased because the reduction of benzaldehyde took place at the same time. On the other hand, reaction of **1** with aliphatic aldehydes proceeded smoothly to give the corresponding δ-amino-β′-hydroxy-β,γ-unsaturated esters (**1b**–**1f**) in excellent yields (Entries 2–6).

A characteristic point of this aldol reaction is that it proceeded with complete α-regioselectivity and formed (*E*)-olefin selectively whereas no diastereoselectivity was observed (*syn*/*anti* = 27/73–57/43).

Then, the same reaction was examined by using other unsaturated aziridines (ketone, amide, and imide) in order to improve

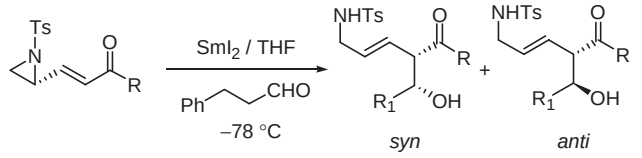
Table 1. SmI_2-mediated aldol reaction of γ,δ-aziridinyl-α,β-unsaturated ester (**1**) and various aldehydes



1 *syn* *anti*

Entry	Aldehyde R	Product	Yield/% (*syn*/*anti*)
1	Ph	**1a**	63 (27/73)
2	Et	**1b**	92 (55/45)
3	$Ph(CH_2)_2$	**1c**	96 (51/49)
4	*i*-Pr	**1d**	86 (56/44)
5	*c*-Hex	**1e**	94 (54/46)
6	Piv	**1f**	97 (57/43)

Table 2. SmI_2-mediated aldol reaction of unsaturated aziridines and 3-phenylpropanal

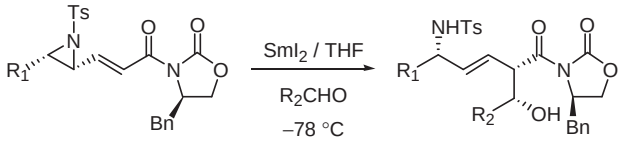


Entry	Aziridine		Product	Yield/%
		R		(*syn*/*anti*)
1	**2**	Ph	**2a**	61 (58/42)
2	**3**	NEt_2	**3a**	83 (60/40)
3	**4**	2-oxazolidinone	**4a**	81 (>95/<5)

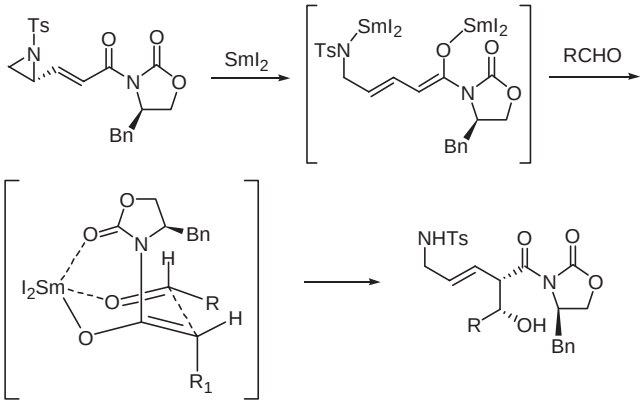
the diastereoselectivity (Table 2). Reactions between other unsaturated aziridines and 3-phenylpropanal also proceeded smoothly and afforded the corresponding δ-amino-β'-hydroxy-β,γ-unsaturated carbonyl compounds in high yields. It is noted that the high *syn* diastereoselectivity was observed (*syn*/*anti* = >95/<5) when unsaturated imide **4** was used (Entry 3).

Prompted by this result, we applied the aldol reaction to the asymmetric one by introducing a suitable chiral auxiliary to the unsaturated aziridine. In the first place, the reaction of (2′*R*,4″*R*,2*E*)-4″-Benzyl-3″-[3-(1′-tosylaziridin-2′-yl)acryloyl]-oxazolidin-2″-one (**5**) with 3-phenylpropanal was examined (Table 3, Entry 1)[9]. This asymmetric aldol reaction proceeded smoothly and afforded the corresponding product **5a** in high yield with high *syn* diastereoselectivity (*syn*/*anti* = >95/<5).[10] In addition, the corresponding products were obtained in high yields with high diasteoselectivities also when other unsaturated aziridines were used (Entries 2–4).

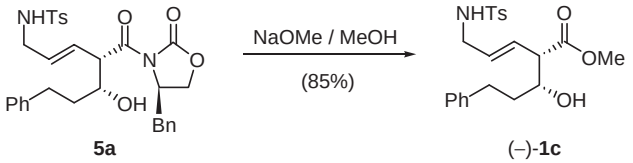
Table 3. SmI_2-mediated asymmetric aldol reaction



Entry	Aziridine	Aldehyde		Product	Yield/%
		R_1	R_2		(*syn*/*anti*)
1	**5**	H	$Ph(CH_2)_2$	**5a**	93 (>95/<5)
2		H	*i*-Pr	**5b**	81 (>95/<5)
3	**6**	Me	$Ph(CH_2)_2$	**6a**	86 (>95/<5)
4		Me	*i*-Pr	**6b**	76 (>95/<5)



Scheme 3.



Scheme 4.

The mechanism of this reaction is shown in Scheme 3. The first step of this reaction involves reduction of the aziridinyl unsaturated imide to cause both fragmentation of an aziridine ring and migration of a double bond and to form the samarium imide enolate, which in turn nucleophilically attacks the aldehyde. Stereochemistry of the reaction could be explained by the chelated six-membered transition state model which contains an additional chelation between oxazolidinone to samarium.

Next, **5a** was converted to enantiomerically pure δ-amino-β'-hydroxy-β,γ-unsaturated ester (–)-**1c**, $[\alpha]_D^{21}$ −27° (*c* 0.26, $CHCl_3$) by methanolysis without accompanying detectable epimerization or double bond conjugation (Scheme 4).

Consequently, the stereoselective synthesis of δ-amino-β'-hydroxy-β,γ-unsaturated esters from γ,δ-aziridinyl-α,β-unsaturated esters and aldehydes was developed via the samarium enolates by using two moles of SmI_2. Further investigation of this reaction is now in progress.

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References and Notes

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8 The stereochemistries of the diastereomers were determined by measuring the coupling constants of their derivatives, which were formed by DIBAL reduction and acetonide formation.
9 Typical experimental procedure is as follows (Table 3, Entry 1): to a mixture of **5** (43.0 mg, 0.0976 mmol) and 3-phenylpropanal (14.5 mg, 0.117 mmol) in THF (3 mL) at −78 °C under an argon atmosphere was added a solution of SmI_2 in THF (0.1 M, 2.40 mL, 0.240 mmol). After the reaction mixture was stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride and was diluted with ethyl acetate. It was extracted with ethyl acetate, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude product was obtained after evaporation of the solvent under reduced pressure and purification by thin-layer chromatography afforded *syn*-adduct (51.3 mg, 93%).
10 The absolute configuration of **5a** was determined by the modified Mosher method.

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