A New Method for the Synthesis of Unsymmetrical Bis-Aldols by the Samarium(II) Iodide-Mediated Aldol Reaction of Aldehydes with Aryl or Alkyl Oxiranyl Ketones

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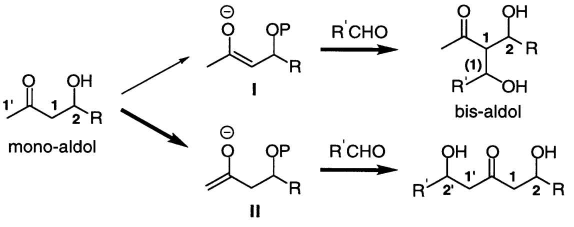
Unsymmetrical alkyl or aryl 2-hydroxy-1-(1-hydroxyalkyl)-alkyl ketones (bis-aldols) were synthesized by the samarium(II) iodide-mediated aldol reaction of aldehydes with alkyl or aryl oxiranyl ketones. Bis-aldols were formed *via* the aldol reaction of aldehydes with samarium enolates generated by epoxy-fragmentation of oxiranyl ketones using two moles of samarium(II) iodide.

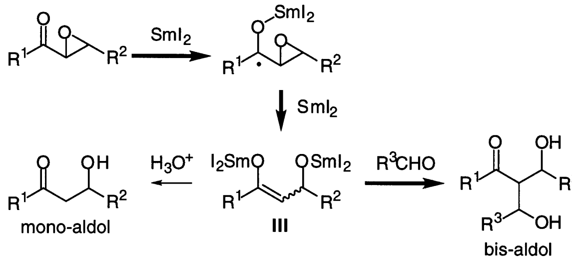
The aldol reaction has long been recognized to be one of the most versatile tools for carbon-carbon bond formation. Therefore, various types of aldol reactions have been developed mostly by the promotion of acids and bases.[1] It was considered that alkyl or aryl 2-hydroxy-1-(1-hydroxyalkyl)alkyl ketones (bis-aldols) were synthesized by the aldol reaction of aldehydes with enolate anions **I** generated from alkyl or aryl 2-hydroxyalkyl ketones (mono-aldols) on treatment with a base. However, it was reported that aldol reaction of aldehydes with enolate anions **II** generated from mono-aldols by deprotonation at 1'-position usually proceeded to afford the isomeric products, 2-hydroxyalkyl 2'-hydroxyalkyl ketones.



Scheme 1.

Though several aldol reactions that formed 2-hydroxyalkyl 2'-hydroxyalkyl ketones were already known, only a few methods for synthesis of bis-aldols were reported because the generation of enolate anions from mono-aldols by selective deprotonation at 1-position using a base had troublesome problems.[2] Namely, treatment of protected mono-aldols with bases usually caused the formation of dehydrated products, α,β-unsaturated ketones, and the treatment of free mono-aldols with strong bases such as LDA also caused retro-aldol reaction. Masamune et al. reported that symmetrical or unsymmetrical alkyl 3-hydroxy-2-(1-hydroxyalkyl)alkanoates (bis-aldolates) were formed by double aldol reaction using 1-phenyl-2-[benzyl(phenylsulfonyl)amino]propyl acetate.[3] In their report, it was noted that alkyl acetates gave the bis-aldolates when *in situ*-formed enol borates,[4] originated from alkyl acetates, are treated with 2-methylpropanal or benzaldehyde.

It is known that a wide range of 1-hydroxy-, 1-acetoxy-, 1-alkoxy-, 1-alkylthio- or 1-halo-alkyl ketones is reduced under mild conditions with 2 molar amounts of SmI_2 to form the corresponding deoxygenated, desulfurated or dehalogenated ketones, respectively.[5,6] It is also reported that reduction of alkyl or aryl oxiranyl ketones with SmI_2 in the presence of a protic compound such as methanol afforded mono-aldols probably *via* samarium enolates **III** as shown in the following scheme.[7] These intermediates, samarium alkoxides **III**, are considered to be the same nucleophilic enolates formed from mono-aldols by deprotonation at 1-position. These results led us to consider that the corresponding bis-aldols would be yielded from alkyl or aryl oxiranyl ketones on treatment with carbonyl compounds, electrophiles, in aprotic solvent *via* the above mentioned samarium enolates **III**.



Scheme 2.

In the first place, the aldol reaction of (3*SR*,2*RS*)-3-methyloxiran-2-yl phenyl ketone (**1**), an aryl oxiranyl ketone, with several aldehydes was examined. The reaction of **1** with benzaldehyde gave the corresponding bis-aldols in good yields along with a small amount of 2-hydroxypropyl phenyl ketone (mono-aldol). Since these bis-aldol adducts have 1,3-diphenyl structure, undesirable elimination of the hydroxyl group at 2-position or retro-aldol reaction took place during the purification according to the usual work up. The desired bis-aldols were obtained up to 70% yield in total when the reaction was carried out at -100 °C for 1 h and at -45 °C for 5 h; however, these bis-aldol adducts were not stable enough to determine their stereochemistry (Table 1, Entry 1). On the other hand, the bis-aldol adducts prepared from **1** with aliphatic aldehydes were relatively stable and their configurations were determined after converting them to the corresponding acetonides (Entries 2-4). When alkyl oxiranyl ketones, (3*SR*,2*RS*)-3-*i*-propyloxiran-2-yl methyl ketone and (3*SR*,2*RS*)-3-phenyloxiran-2-yl methyl ketone, were used as substrates for the generation of samarium enolates, the corresponding bis-aldols were obtained in high yields (Entries 7-9). In these cases, undesirable formation of α,β-unsaturated ketones did not take place because bis-aldol adducts were relatively stable.

Concerning diastereoselectivities of the present reaction, it was proven that the two stereoisomers **A** and **D** were produced (Entries 2-9). For example, aldol reaction of **1** with propanal afforded the corresponding **A** as a major stereoisomer and **D** as a minor stereoisomer as shown in Table 1 (Entry 2, **A** / **D** = 67 / 33). The configurations of **A** and **D** were confirmed as *syn,syn* and *anti,anti* by measuring ^{1}H NMR of the corresponding acetonide derivatives.

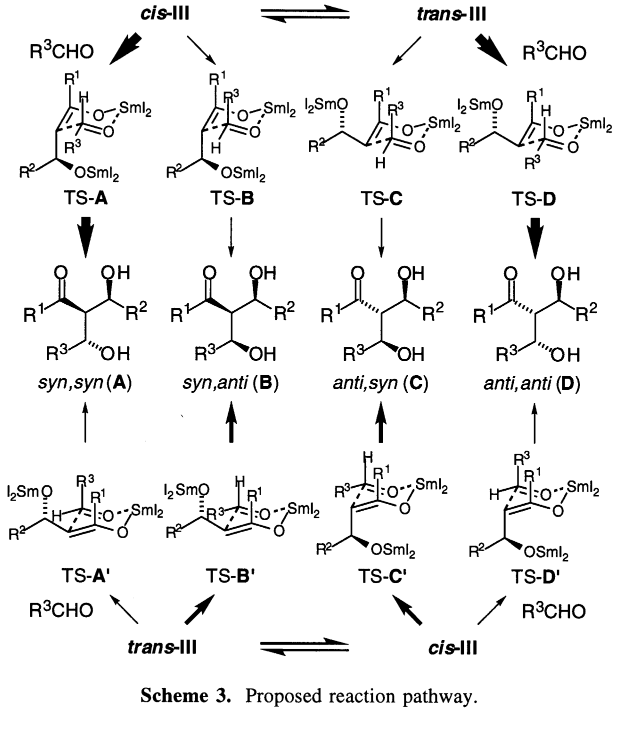
Table 1. Yields of several bis-aldols

Entry	R^1	R^2	R^3	Yield / % (**A** / **B** / **C** / **D**)[a]
1	Ph	Me	Ph	70 (nd)
2	Ph	Me	Et	75 (67 / 0 / 0 / 33)
3	Ph	Me	$Ph(CH_2)_2$	83 (61 / 0 / 0 / 39)
4	Ph	Me	*i*-Pr	88 (40 / 0 / 0 / 60)
5	Ph	*n*-Pr	$Ph(CH_2)_2$	90 (35 / 0 / 0 / 65)
6	Ph	*n*-Pr	*i*-Pr	84 (50 / 0 / 0 / 50)
7	Me	*i*-Pr	Et	85 (88 / 0 / 0 / 12)
8	Me	*i*-Pr	$Ph(CH_2)_2$	95 (75 / 0 / 0 / 25)
9	Me	Ph	$Ph(CH_2)_2$	84 (60 / 0 / 0 / 40)

[a] The ratio of possible four isomers was determined by integration of the ^{1}H NMR spectrum of the mixture of corresponding acetonide derivatives.

It is assumed then that a mixture of two isomeric disamarium alkoxy enolates **III** is generated from alkyl or aryl oxiranyl ketones by the reduction with SmI_2 at first. The reaction is considered to proceed through Zimmermann-type transition states; therefore, *syn,syn*-bis-aldol **A** would be produced from *cis*-**III** *via* TS-**A** while *anti,anti*-bis-aldol **D** would be produced from *trans*-**III** *via* TS-**D** as shown in Scheme 3.

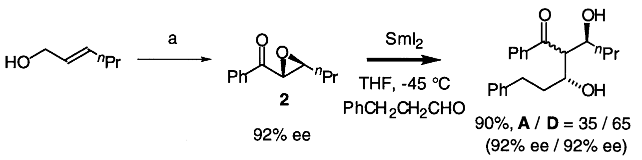
A typical experimental procedure is described for the reaction of **1** and 3-phenylpropanal: to a mixture of **1** (81 mg, 0.50 mmol) and 3-phenylpropanal (74 mg, 0.55 mmol) in THF (5 mL) at -78 °C under an argon atmosphere was added a solution of SmI_2 in THF (0.1 M, 11 mL, 1.1 mmol). After the reaction mixture was stirred for 1 h at -78 °C and for 5 h at -45 °C, the reaction mixture was quenched with water and was diluted with ethyl acetate. It was filtered through a short pad of silica gel and the filtrate was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, crude product was purified by silica gel chromatography to give a mixture of the corresponding bis-aldols (124 mg, 83%) as a colorless oil (Table 1, Entry 3).



Scheme 3. Proposed reaction pathway.

In the next place, reaction of a chiral aryl oxiranyl ketone with an aldehyde was tried in the presence of SmI_2. The chiral oxiranyl ketone, (3*S*,2*R*)-3-propyloxiran-2-yl phenyl ketone (**2**), was prepared according to the following procedure: epoxidation of (*E*)-2-hexen-1-ol with $\mathrm{Ti(O}^i\mathrm{Pr)_4}$ / ^{t}BuOOH / L-(+)-diethyl tartrate led to 79% isolated yield of ((2*S*,3*S*)-3-propyloxiran-2-yl)methanol according to Sharpless method.[8] The subsequent Swern oxidation gave (3*S*,2*R*)-3-propyloxirane-2-carbaldehyde, which was in turn treated with phenyllithium to afford the corresponding secondary alcohol. The second Swern oxidation led to the desired ketone **2** (92% ee by HPLC analysis).

Treatment of the mixture of optically active **2** and 3-phenylpropanal with SmI_2 under the standard reaction conditions gave two separable diastereomers of 2-hydroxy-1-(1-hydroxy-3-phenylpropyl)pentyl phenyl ketone (90%, *syn,syn* (**A**) / *anti,anti* (**D**) = 35 / 65). It was noteworthy that the excellent optical purity of produced bis-aldols was preserved through the present protocol (determined by HPLC; 92% ees, respectively).



Scheme 4. Reagents and conditions: a) $\mathrm{Ti(O}^i\mathrm{Pr)_4}$, ^{t}BuOOH, (+)-DET, CH_2Cl_2, -23 °C (79%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to -23 °C (88%); PhLi, THF, -78 °C (76%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to -23 °C (92%).

Thus, a convenient method was developed for the synthesis of unsymmetrical bis-aldols from alkyl or aryl oxiranyl ketones and aldehydes by using 2 moles of SmI_2 *via* the disamarium alkoxy enolates.

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References and Notes

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5 G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986).

6 Aldol-type *C*-glycosidation of phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-arabino-hexopyranosid-2-ulose was reported in 1998 by utilizing SmI_2. The reaction probably proceeded through the initial formation of samarium enolate by the desulfurization at C-1 position with SmI_2, which in turn reacted with carbonyl compounds to form the corresponding aldol-type products. S. Ichikawa, S. Shuto, and A. Matsuda, *Tetrahedron Lett.*, **39**, 4525 (1998).

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