A Convenient Method for the Preparation of Unsymmetrical Bis-Aldols by Way of Sequential Two Aldol Reactions

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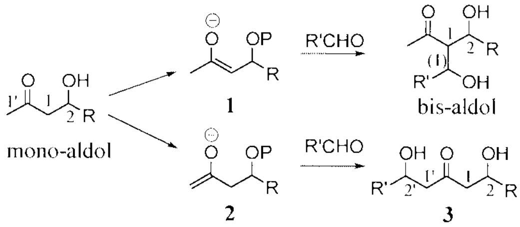
Unsymmetrical alkyl 2-hydroxy-1-(1-hydroxyalkyl)alkyl ketones (bis-aldols) are successfully synthesized by way of sequential two aldol reactions using α-bromo ketones and two different aldehydes. In the first reaction, α-bromo-β-stannyloxy ketones are formed by tin(II) trifluoromethanesulfornate-promoted aldol reaction of α-bromo ketones with several aldehydes. Bis-aldols are then formed via the second aldol reaction between another aldehydes and dianionic enolates generated by the reduction of α-bromo-β-metalloxy ketones with titanium(IV) iodide and copper.

The aldol reaction has long been recognized to be one of the most versatile carbon–carbon bonds forming tools. Therefore, various types of aldol reaction that were mostly promoted by acids and bases have been developed by many research groups.[1] It was considered that alkyl or aryl 2-hydroxy-1-(1-hydroxyalkyl)alkyl ketones (bis-aldols) would be synthesized by the addition of aldehydes to enolate anions **1** generated from alkyl or aryl 2-hydroxyalkyl ketones (mono-aldols) on treatment with a base.

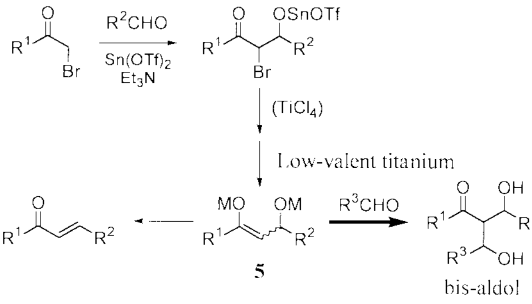


Scheme 1.

In general, however, the undesirable reaction of aldehydes with enolate anions **2** generated from mono-aldols by deprotonation at 1'-position proceeded to afford 2-hydroxyalkyl 2'-hydroxyalkyl ketones **3**, isomeric products of the bis-aldols. Though several reactions that formed **3** were already known, only a few examples for the synthesis of bis-aldols were reported because the generation of enolate anions **1** by selective deprotonation at 1-position of mono-aldols with bases had some problems.[2–4] Namely, a formation of dehydrated products, α,β-unsaturated ketones, was caused by treating protected mono-aldols with bases, and a retro-aldol reaction was caused by treating free mono-aldols with strong bases such as LDA. Therefore, development of a general and effective method for the preparation of bis-aldols was strongly required.

Although the enolates **1** were considered to be formed selectively by the reduction of α-halo-β-hydroxy ketones **4** using a low-valent metal species, the reaction of these silylated derivatives, α-bromo-β-siloxy ketones, was tried at first since **4** were generally unstable. However, when the aldol reaction of 3-bromo-6-phenyl-4-(*t*-butyldimethylsiloxy)hexan-2-one[5] with 3-phenylpropionaldehyde using a low-valent metal generated from $ZnCl_2$, $SnCl_2$ or $TiCl_2$ was tried,[6,7] only 6-phenyl-3-hexen-2-one was obtained probably via desilyloxylation of the corresponding enolate anion.

Next, it was considered that *in situ* formed dimetal enolate **5** would prevent the above-mentioned β-elimination since metalloxy group was generally known to be hardly eliminated. Then, the synthesis of bis-aldols was tried by the following sequential reactions: a $Sn(OTf)_2$-mediated aldol reaction of bromoacetone with 3-phenylpropionaldehyde,[8] followed by treatment of the adduct with a low-valent metal (Scheme 2).



Scheme 2.

After the reaction, it was observed that β-elimination also took place when a low-valent metal generated from $ZnCl_2$, $SnCl_2$ or $TiCl_2$ was used since the reduction proceeded above 0 °C. In the case when the *in situ* formed low-valent titanium iodide species generated from TiI_4 and Cu was used at –30 °C in the second aldol reaction with isobutyraldehyde, a mixture of stereoisomers of the desired bis-aldol was obtained in 64% yield along with the by-product (30%). On the other hand, the second reaction proceeded smoothly at –78 °C when pivalonitrile was used as an additive, and almost no undesirable α,β-unsatuated ketone was detected.[7b] In the similar fashion, the corresponding bis-aldols were obtained in good yields using several α-bromo ketones and aldehydes as summarized in Table 1.

Concerning diastereoselectivities, it was proved in the present reaction that stereoisomers **A** and **B** were produced together with **D** as a major product (Method A). The configurations of **A**, **B** and **D** were confirmed as *syn,syn*; *syn,anti;* and *anti,anti*; respectively by measuring ^{1}H NMR of their acetonide derivatives. It is assumed then that a mixture of two isomeric dimetal enolates **5** (*cis* and *trans*) is generated from α-bromo-β-metalloxy ketones first by the reduction with a low-valent titanium species. The reaction is considered to proceed through Zimmermann-type transition states; therefore, **A, B** and **D** would be mainly produced from *cis*-**5** via TS-**A**, from *trans*-**5** via TS-**B'** and from *trans*-**5** via TS-**D**, respectively, as shown in Scheme 3. The metal enolates might exist in almost *trans*-**5** forms in the above cases because **D** was mainly obtained. It is very interest-

Table 1. Yields of several bis-aldols

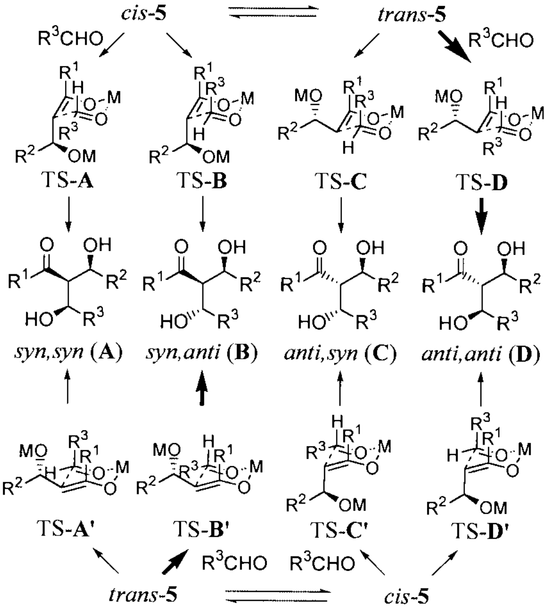
Entry	R^1	R^2	R^3	Yield / %	$(\mathbf{A} / \mathbf{B} / \mathbf{C} / \mathbf{D})^a$	Method^b
1	Me	$Ph(CH_2)_2$	^{i}Pr	88	(10 / 30 / 0 / 60)	A
2	Me	$Ph(CH_2)_2$	^{i}Pr	84	Only **D**	B
3	Me	^{i}Pr	$Ph(CH_2)_2$	87	(15 / 15 / 0 / 70)	A
4	Me	^{i}Pr	$Ph(CH_2)_2$	86	Only **D**	B
5	Me	$Ph(CH_2)_2$	Ph	91	(15 / 20 / 0 / 65)	A
6	Me	$Ph(CH_2)_2$	Ph	93	(0 / 10 / 0 / 90)	B
7	Me	Ph	$Ph(CH_2)_2$	86	(15 / 25 / 0 / 60)	A
8	Me	Ph	$Ph(CH_2)_2$	84	(0 / 15 / 0 / 85)	B
9	Et	$Ph(CH_2)_2$	^{i}Pr	82	(15 / 20 / 0 / 65)	A
10	Et	$Ph(CH_2)_2$	^{i}Pr	87	Only **D**	B
11	Et	^{i}Pr	$Ph(CH_2)_2$	83	(20 / 20 / 0 / 60)	A
12	Et	^{i}Pr	$Ph(CH_2)_2$	79	Only **D**	B
13	^{i}Pr	$Ph(CH_2)_2$	^{i}Pr	84	(25 / 15 / 0 / 60)	A
14	^{i}Pr	$Ph(CH_2)_2$	^{i}Pr	86	Only **D**	B
15	^{i}Pr	^{i}Pr	$Ph(CH_2)_2$	82	(20 / 10 / 0 / 70)	A
16	^{i}Pr	^{i}Pr	$Ph(CH_2)_2$	78	Only **D**	B

[a] The ratio of the possible four isomers was determined by integration of the ^{1}H NMR spectrum of a mixture of the corresponding dimethyl acetonide derivatives. [b] Method A: No $TiCl_4$ was added after the first reaction. Method B: 1.2 molar amounts of $TiCl_4$ were added after the first reaction.

ing point that SmI_2-mediated bis-aldol formation from epoxy ketones with aldehydes, which was recently developed by our group, gave the stereoisomers **A** and **D**, predominantly.[9]

After the first aldol reaction, 1.2 molar amounts of $TiCl_4$ were added in order to form titanium alkoxide from initially formed stannous alkoxide by transmetallation and then the second aldol reaction was performed. By this procedure (Method B), only one stereoisomer **D** was obtained in the case of using aliphatic α-bromo ketones and two different aliphatic aldehydes while two stereoisomers **D** and **B** were obtained in the ratios of > 85/15 when benzaldehyde was used as one of the electrophiles (Entries 6 and 8). Therefore, it was shown that the intermediate titanium enolates in the method B exist mostly in their *trans* forms.

The typical procedure of method B for the reaction of bromoacetone, 3-phenylpropionaldehyde and isobutyraldehyde is described: to a mixture of $Sn(OTf)_2$ (304 mg, 0.73 mmol) and triethylamine (0.1 mL, 0.70 mmol) in CH_2Cl_2 (8 mL) was added dropwise bromoacetone (97 mg, 0.70 mmol) under an argon atmosphere at –78 °C. After the reaction mixture had been stirred for 1 h, 3-phenylpropionaldehyde (89 mg, 0.66 mmol) was added at –78 °C. The reaction mixture was stirred for 1 h at the same temperature, and then $TiCl_4$ (151 mg, 0.80 mmol) was added at -90 °C. After the reaction mixture had been stirred for 1 h, supernatant CH_2Cl_2 solution (0.1 M, 8.0 mL, 0.80 mmol), prepared by stirring of TiI_4 (1.00 g, 1.80 mmol) and Cu (286 mg, 4.50 mmol) in the existence of pivalonitrile (1.0 mL, 9.0 mmol) in CH_2Cl_2 (17 mL), and isobutyraldehyde (57 mg, 0.80 mmol) were respectively added at –90 °C. The reaction mixture was stirred for 1 h at –90 °C and 3 h at –78 °C, and then phosphate buffer solution (pH = 7) was added. After filtration of the mixture through a short pad of Celite, the filtrate was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by silica gel chromatography to give the desired bis-aldol **D** (147 mg, 84%) as a colorless oil (Table 1, Entry 2).



Scheme 3. Proposed reaction pathway.

Thus, a convenient method for the synthesis of unsymmetrical bis-aldols by way of sequential two aldol reactions using α-bromo ketones and two different aldehydes was developed.

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