A Novel Synthesis of *syn* and *anti* β-Hydroxy Dithioacetals, Masked Cross-Aldols between Aldehydes

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Ketene dithioacetals readily reacted with aldehydes in the presence of a Lewis acid such as $BF_3 \cdot OEt_2$ or TMSOTf to generate the cationic adducts, which in turn reacted with $NaAlH_2(OCH_2CH_2OCH_3)_2$, leading to the corresponding β-hydroxy dithioacetals, masked cross-aldols between aldehydes. Each diastereomer was selectively obtained by choosing the appropriate Lewis acid and substituents on the sulfur atoms of the ketene dithioacetals.

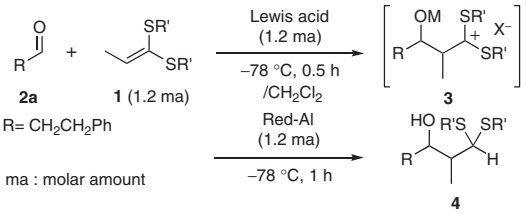
The aldol reaction is one of the most versatile methods for formation of carbon–carbon bonds in organic synthesis.[1] Although many successful examples of cross-aldol type reactions have been reported, the synthesis of β-hydroxy aldehydes by the aldol reaction between two different aldehydes still remains troublesome.[2] It is due to problematic reactions such as (1) self-aldol reaction, (2) poly-aldolization, and (3) Tishchenko-type reaction and also the instability of the products toward (4) dehydration and (5) oligomerization. There have been reported only limited examples of cross-aldol reactions between aldehydes, which were conducted by using a proline catalyst[3] or via titanium[4] or trichlorosilyl[5] enolates. A few derivatives of the β-hydroxy aldehydes such as acetals,[5] hydrazones,[6] and oximes[7] have been prepared as their synthetic equivalents. Thus, the synthesis of β-hydroxy aldehydes and their derivatives still represents a challenging task.

In this context, β-hydroxy dithioacetals are attractive aldol equivalents, because dithioacetals are widely used not only as protected carbonyl compounds but also as reactive intermediates in synthetic reactions, such as deoxygenation of carbonyl compounds, elimination leading to vinyl sulfides, and generation of acyl anion equivalents. In spite of these synthetic utilities, so far few examples are known for the synthesis of β-hydroxy dithioacetals[8] from aldehydes.

Recently, we have developed an efficient carbon extension reaction of acetals or aldehydes by using ketene dithioacetals and nucleophiles,[9] which allows three-component coupling in a one-pot procedure. The reaction of ketene dithioacetals with acetals or aldehydes is promoted by TMSOTf, followed by the addition of carbon nucleophiles, such as alkylmetals and metal enolates, leading to highly functionalized dithioacetals. This reaction prompted us to explore its application to the synthesis of β-hydroxy dithioacetals, that is masked cross-aldol adducts between aldehydes, by using a hydride as a nucleophile of the third component. In this communication, we wish to report a novel method for the diastereoselective synthesis of β-hydroxy dithioacetals from ketene dithioacetals, aldehydes, and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).

Choosing the reaction of methylketene dithioacetal **1** with 3-phenylpropanal **2** and Red-Al as a model reaction, we examined the effects of (1) Lewis acids such as TMSOTf, TfOH, $TiCl_4$, $GaCl_3$, and $BF_3 \cdot OEt_2$ and (2) substituents on the sulfur atoms of **1** on the yield and the diastereoselectivity of β-hydroxy dithioacetals **4**. The results revealed that the combination of a Lewis acid and substituents of the dithioacetal moiety greatly affects the diastereomer ratios of the products ranging from *syn*/*anti* = 76/24 to *syn*/*anti* = 18/82. As shown in Table 1, TMSOTf was proved to be the Lewis acid of choice to afford the corresponding dithioacetal **4** in good yield with good *syn* selectivity, when cyclic dithioacetal **1b** was reacted with **2a** at −94 °C (Entry 3). On the other hand, *anti* β-hydroxy dithioacetal **4** was obtained as a major product in good yield by the use of $BF_3 \cdot OEt_2$ for diethyl dithioacetal **1a** instead of the cyclic **1b** (Entry 5). Other ketene dithioacetals such as dimethyl and diisopropyl dithioacetals were not effective in improving the yield and the stereoselectivity. Treatment of methylketene diphenyl dithioacetal **1** (R′ = Ph) and **2a** with TMSOTf provided **4** with high diastereoselectivity (*syn*/*anti* = 94/6), albeit in low yield (18%).

Table 1. Effects of Lewis acids and substituents of the dithioacetal moiety



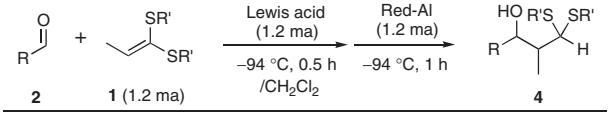
Entry	Lewis acid	R'	Yield /% (*syn*/*anti*)[a]
1	TMSOTf[b]	Et (**1a**)	78 (61/39) (**4a**)[c]
2		–$(CH_2)_3$– (**1b**)	77 (73/27) (**4b**)
3[d]		–$(CH_2)_3$– (**1b**)	**74** (**76**/24) (**4b**)
4	$BF_3 \cdot OEt_2$	Et (**1a**)	75 (23/77) (**4a**)
5[d]		Et (**1a**)	**74** (18/**82**) (**4a**)
6		–$(CH_2)_3$– (**1b**)	76 (70/30) (**4b**)

[a]See Ref. 10. [b]The crude mixture was treated with 1 M HCl aq in THF at rt for 1 h. [c]See Ref. 11. [d]The reaction was conducted at −94 °C.

In order to expand the scope of this reaction, the diastereoselective synthesis of several other β-hydroxy dithioacetals **4** was examined by using other aldehydes **2**. Most of the examined aldehydes reacted smoothly at −94 °C to afford the corresponding dithioacetals in good yield with good *syn* or *anti* diastereoselectivity in accord with the tendency of the above results affording **4a** and **4b** (Table 2).[12] While the reaction of *trans*-cinnamaldehyde (**2d**) with **1b** in the presence of $BF_3 \cdot OEt_2$ gave a 17% yield of **4** along with byproducts such as a 1,4-addition product and a [2+2] cycloaddition product, the desired reaction was promoted by t-$BuMe_2SiOTf$ (TBSOTf) to afford **4** in good yield with high *anti*-selectivity (*syn*/*anti* = 10/90, Entry 5).

In addition, a similar reaction using a nonsubstituted ketene dithioacetal **5** was investigated to provide dithioacetal **6**, which is an equivalent of the cross-aldol product derived from an acetaldehyde enolate. While treatment of ketene diethyl acetal and aldehyde **2a** with TMSOTf or $BF_3 \cdot OEt_2$ gave the desired product in 57 or 54% yield, cyclic ketene dithioacetal **5** improved the yield of the product **6** (69 or 76%), respectively. Furthermore, $TiCl_4$ raised the yield of **6** up to 79% (Scheme 1). The reactions of nonsubstituted ketene dithioacetals have been limited, probably due to their propensity for polymerization under strongly acidic conditions. Thus, it is noteworthy that the carbon–carbon bond formation of nonsubstituted ketene dithioacetal **5** has been cleanly effected under Lewis acid conditions without its polymerization.

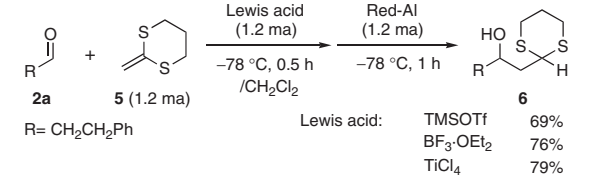
Table 2. Synthesis of β-hydroxy dithioacetals **4**



2 **1** (1.2 ma) **4**

Entry	R		Yield /% (*syn*/*anti*) TMSOTf (1.2 ma)[a] R′ = –$(CH_2)_3$– (**1b**)	$BF_3 \cdot OEt_2$ (2.4 ma) R′ = Et (**1a**)
1	$PhCH_2CH_2$	(**2a**)	74 (**76**/24)	81 (18/**82**)
2	*i*-Pr	(**2b**)	58 (**73**/27)[b]	70 (27/**73**)
3	Ph	(**2c**)	74 (**81**/19)	61 (23/**77**)
4	Ph	(**2d**)	73 (**65**/35)[b]	80 (24/**76**)[b,c]
5			—	65 (10/**90**)[d]

[a]The crude mixture was treated with 1 M HCl aq in THF at rt for 1 h. [b]The reaction was coducted at −78 °C. [c]TMSOTf (1.2 ma) was used. [d]TBSOTf (1.2 ma) was used.



Scheme 1. A reaction of nonsubstituted ketene dithioacetal **5**.

In summary, a novel method for the synthesis of β-hydroxy dithioacetals has been established. The dithioacetals are obtained in good yield in a one-pot procedure from ketene dithioacetals and aldehydes on successive treatment with TMSOTf or $BF_3 \cdot OEt_2$ and then Red-Al. Furthermore, each diastereomer can be synthesized in good selectivity simply by choosing one of the two optimized procedures. This method provides the equivalents of β-hydroxy aldehydes, which have a useful skeleton for the synthesis of functionalized compounds.

A typical experimental procedure is as follows: To a solution of **2a** (40 mg, 0.30 mmol) and **1b** (59 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL) was added $BF_3 \cdot OEt_2$ (0.091 mL, 0.72 mmol) at −94 °C. After the reaction mixture was stirred at −94 °C for 0.5 h, Red-Al in toluene (3.67 M, 0.098 mL, 0.36 mmol) was added at −94 °C. After stirring at −94 °C for 1 h, the reaction was quenched with phosphate buffer (pH 7). The aqueous layer was extracted with EtOAc three times, and the combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the resulting residue was purified by preparative TLC on silica gel (Hexane–EtOAc (10:1)) to afford the desired product **4** (R = CH_2CH_2Ph, R′ = –$(CH_2)_3$–; 71 mg, 81%, *syn*/*anti* = 18/82).

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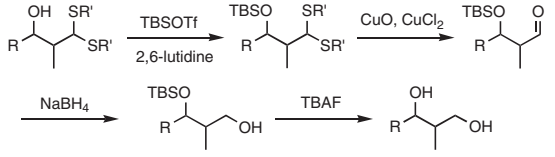
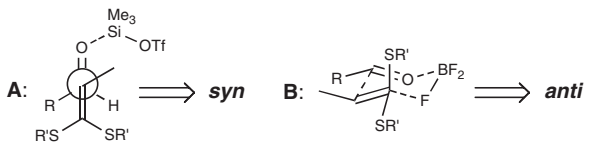
10 The stereochemistries of β-hydroxy dithioacetals **4** were determined by their derivatization to the corresponding 1,3-diols with defined structures as shown below.[13]



11 There was an error in determining the stereochemistry of compound **13** in Scheme 1 in our previous report.[9] The correct diastereoselectivity is given in Table 1, Entry 1 in this communication.

12 The tendency of the *syn*/*anti* selectivity can be explained by assuming open transition structure **A** and cyclic transition structure **B** where the fluorine of BF_3 is coordinated to the carbocationic center.[14]



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