# Lewis Base Activation of Lewis Acids: Catalytic Enantioselective Glycolate Aldol Reactions**

Scott E. Denmark and *Won-jin Chung*

Chiral 1,2-diols are ubiquitous subunits in natural products and in chiral ligands used for asymmetric catalysis. In addition, a variety of useful structures can be accessed by chemical transformations of 1,2-diols. Whereas *syn*-1,2-diols can be prepared with high enantioselectivities by Sharpless asymmetric dihydroxylation of olefins,[1] *anti*-1,2-diols can be synthesized by asymmetric epoxidation and ring opening.[2] These oxidation reactions represent powerful methods for vicinal functionalization of geometrically defined alkenes because of the highly stereospecific nature of these methods.

The glycolate aldol reaction is a conceptually distinct route to the preparation of stereodefined 1,2-diol units in which the bond between the vicinal diol and both stereogenic centers are formed as part of the process concomitantly (Scheme 1). In principle, the selective formation of either diastereomer by this type of reaction is possible. Moreover, it is not necessary to control the geometry of the double bonds because of the stereoconvergent nature of Mukaiyama-type aldol reactions.[3]
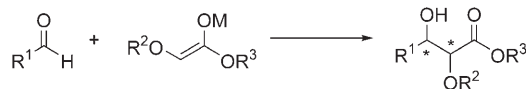
Scheme 1. Glycolate aldol reaction.

Stereoselective glycolate aldol reactions are most commonly performed with chiral oxazolidinone derivatives of glycolate esters.[4] In general, *syn*-1,2-diols are obtained as the major diastereomers through boron-mediated aldolizations. Recently, a few systematic studies of auxiliary-directed *syn*- or *anti*-selective glycolate aldol reactions have been described.[5] However, catalytic stereoselective glycolate aldol reactions are very rare. The only successful examples have been reported by Kobayashi et al.[6] Although highly selective formation of both diastereomers is achieved by changing both the geometry of ketene acetals and the structure of chiral

[*] Prof. S. E. Denmark, W.-j. Chung
Department of Chemistry
University of Illinois
Urbana, IL, 61801 (USA)
Fax: (+1) 217-333-3984
E-mail: denmark@scs.uiuc.edu
Homepage: http://www.scs.uiuc.edu/denmark/

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amine ligands, it is necessary to employ an excess of tin reagents and a stoichiometric amount of the chiral amine in some cases. Moreover, slow addition of the tin reagents over several hours with a syringe pump is required. Thus, an efficient and practical catalytic enantioselective glycolate aldol reaction remains a challenge.

Previous studies from our group have demonstrated the utility of Lewis base catalyzed, Lewis acid mediated, enantioselective Mukaiyama-type aldol reactions utilizing $SiCl_4$ and bisphosphoramide catalyst (*R,R*)-**1** (Figure 1).[7] This catalyst system is effective for the addition of aldehyde-, ketone-, acetate-, or propanoate-derived enoxysilanes. Interestingly, the aldol additions of substituted silyl ketene acetals are highly *anti*-selective, although the rate and selectivity are sensitive to the size of the α-carbon substituent and the ester group. Herein, we describe the first diastereodivergent, catalytic, enantioselective glycolate aldol reaction.
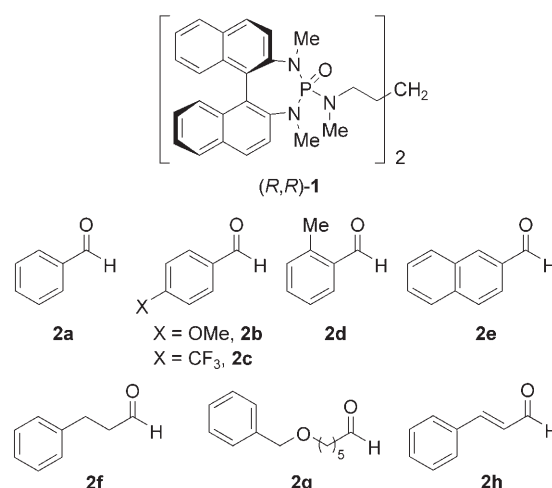
Figure 1. Structures of catalyst and aldehydes.

An extensive survey of hydroxy protecting groups, ester moieties, and silyl derivatives revealed that trimethylsilyl (TMS) ketene acetal **3a**, prepared from a methyl glycolate that is affixed with a large (cumyl) protecting group on the α-oxygen atom, leads to high *syn* selectivity in the glycolate aldol reaction. For example, **3a** reacted with benzaldehyde (**2a**) in the presence of $SiCl_4$ (1.1 equiv) and (*R,R*)-**1** (1 mol%) to afford the *syn*-aldol product **4aa** after 0.5 hours in high diastereoselectivity and enantioselectivity (Table 1, entry 1). The *syn*-selective glycolate aldol reaction is general for a range of structurally and electronically diverse aromatic aldehydes. Excellent chemical yields and stereoselectivities were consistently obtained from electron-rich 4-

Table 1: *syn*-Selective glycolate aldol reactions with aromatic aldehydes.[a]

Entry	RCHO	*t* [h]	Product	Yield [%][b]	d.r.[c]	e.r.[d]
1	**2a**	0.5	**4aa**	87	99:1	96.6:3.4
2	**2b**	1.5	**4ab**	98	99:1	97.7:2.3
3	**2c**	0.5	**4ac**	99	99:1	98.0:2.0
4	**2d**	9.0	**4ad**	93	98:2	96.8:3.2
5	**2e**	0.5	**4ae**	94	>99:1	98.5:1.5

[a] Reaction conditions: silyl ketene acetal (1.2 equiv), SiCl₄ (1.1 equiv), and *i*Pr₂NEt (0.1 equiv) at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution over 15 min. [b] Yields of analytically pure material. [c] Determined by ¹H NMR analysis of HC2 or HC3. [d] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC).

methoxybenzaldehyde (**2b**), electron-poor 4-trifluoromethyl-benzaldehyde (**2c**), sterically hindered 2-tolualdehyde (**2d**), and bicyclic 2-naphthaldehyde (**2e**) (Table 1, entries 2–5). However, the reactivity was significantly influenced by steric encumbrance in the aromatic aldehyde as demonstrated by the reduced reactivity of **2d**.

Remarkably, the stereochemical course of this reaction could be completely reversed by changing the size of the substituents on the silyl ketene acetal. *tert*-Butyldimethylsilyl (TBS) ketene acetal **3b**, derived from the 3-methyl-3-pentyl ester of α-methoxyacetic acid, reacted with benzaldehyde (**2a**) to give the *anti*-aldol product **4ba** in high diastereoselectivity and enantioselectivity (Table 2, entry 1). The generality of *anti*-selective glycolate aldol reaction was also shown for a series of aromatic aldehydes. Electron-rich 4-methoxybenzaldehyde (**2b**), electron-poor 4-trifluoromethyl-benzaldehyde (**2c**), *o*-substituted 2-tolualdehyde (**2d**), as well as bicyclic 2-naphthaldehyde (**2e**) provided products in high yields and stereoselectivities (Table 2, entries 2–5). Again, the decreased reactivity of **2d** was observed. All attempts to replace the methyl group on the α-oxygen atom to more readily removable groups were unsuccessful.

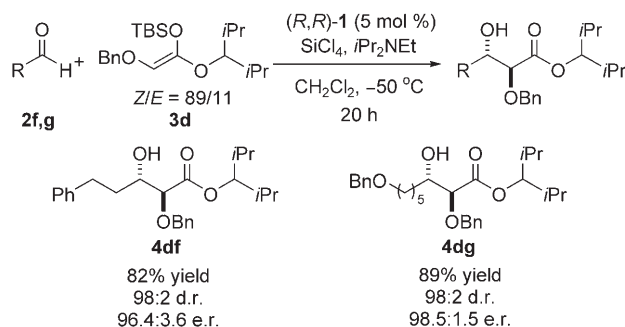**Table 2:** *anti*-Selective glycolate aldol reactions with aromatic aldehydes.[a]

Entry	RCHO	*t* [h]	Product	Yield [%][b]	d.r.[c]	e.r.[d]
1	**2a**	0.5	**4ba**	91	>99:1	95.1:4.9
2	**2b**	3.0	**4bb**	93	>99:1	98.3:1.7
3	**2c**	0.5	**4bc**	96	>99:1	98.3:1.7
4	**2d**	18.0	**4bd**	91	98:2	93.1:6.9
5	**2e**	0.5	**4be**	93	>99:1	97.4:2.6

[a] Reaction conditions: silyl ketene acetal (1.2 equiv), SiCl₄ (1.1 equiv), and *i*Pr₂NEt (0.1 equiv) at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution over 15 min. [b] Yields of analytically pure material. [c] Determined by ¹H NMR analysis of HC2 or HC3. [d] Determined by CSP-SFC methods.

Unfortunately, neither **3a** nor **3b** underwent aldol reactions with hydrocinnamaldehyde (**2f**) even after 20 hours in the presence of 5 mol% of (*R,R*)-**1** at −50°C and a concentration of 0.4 M. The attenuated reactivity of aliphatic aldehydes has been a persistent problem in the Lewis base catalyzed, SiCl₄-promoted carbonyl addition reactions.[7] However, the effect of substituents on the rate and selectivity allowed a suitable reaction partner to be found. Silyl ketene acetal **3c**[8] was sufficiently reactive to undergo aldol reaction with **2f** in a considerably improved yield (Scheme 2); acceptable *syn* diastereoselectivity and enantioselectivity were also obtained.
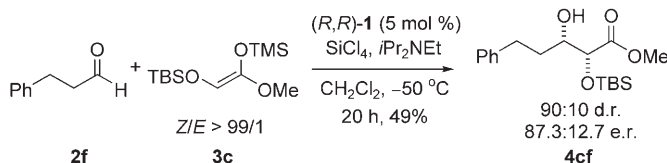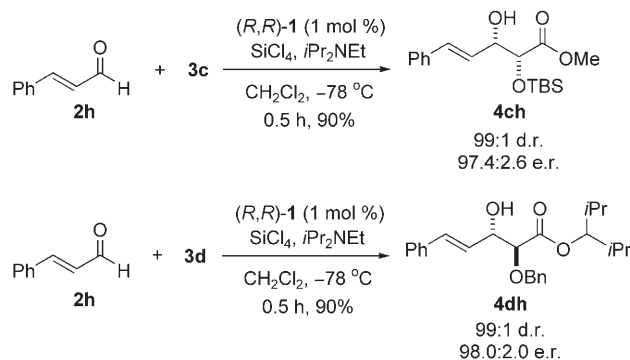

Scheme 2. *syn*-Selective glycolate aldol reaction with an aliphatic aldehyde.

In the *anti*-selective reaction manifold, the reactivity of the silyl ketene acetal could be enhanced by replacing the bulky tertiary ester with a bulky secondary ester. Silyl ketene acetal **3d** reacted smoothly with **2f** to afford the corresponding *anti*-aldol product **4df** in high yield and stereoselectivity (Scheme 3). In this case, the more synthetically useful benzyl group, as opposed to the methyl group, could be employed to protect the α-oxygen atom. Another primary aliphatic aldehyde, 6-benzyloxyhexanal (**2g**), was also a suitable substrate which provided *anti*-aldol product **4dg** in high yield and excellent stereoselectivity.
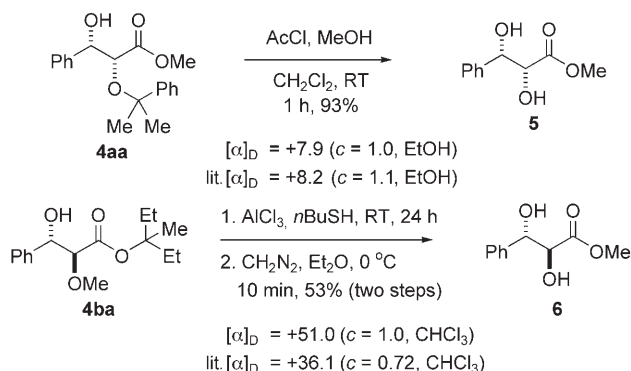

Scheme 3. *anti*-Selective glycolate aldol reactions with aliphatic aldehydes; Bn = benzyl.

Silyl ketene acetals **3c** and **3d** also underwent aldol addition with an alkenyl aldehyde (Scheme 4). The reactions of **3c** and **3d** with *E*-cinnamaldehyde (**2h**) afforded the *syn*- and *anti*-aldol products, respectively, in high yields with excellent diastereo- and enantioselectivities.

The absolute and relative configurations of **4aa** and **4ba** were established by chemical correlations to known compounds **5**[9] and **6**[10] (Scheme 5). The *S* configurations at C3 imply a *Re* face attack on the aldehyde. This sense of

Scheme 4. *syn-* and *anti-*Selective glycolate aldol reactions with an alkenyl aldehyde.

Scheme 5. Absolute configuration determinations.

asymmetric induction is in agreement with previous results from the same catalytic system.[7]

In conclusion, an efficient, Lewis base catalyzed, stereoselective glycolate aldol reaction has been developed for a wide range of aldehydes. Remarkably, both *syn-* and *anti-*1,2-diols can be obtained under the same catalytic system by modulating the size of the substituents on the silyl ketene acetal. Additional studies are underway to elucidate the origin of the remarkable switch of diastereoselectivity.

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