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Synthetic utility of bowl-shaped tris(2,6-diphenylbenzyl)silyl glyoxylate as a stable glyoxylate: application to highly diastereoselective aldol reactions

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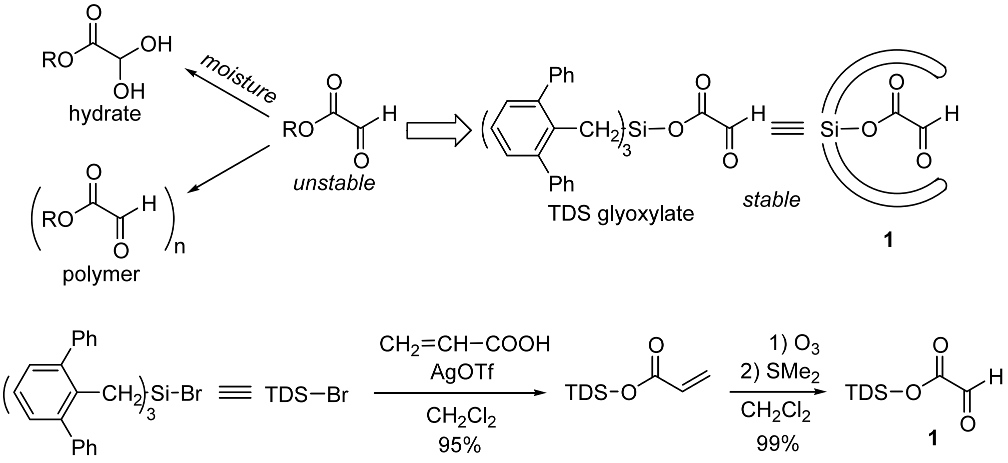
Abstract—A stable glyoxylate can be successfully applied to both *syn*- and *anti*-selective aldol reactions by using two different kinds of ordinary Lewis acids. Thus, treatment of bowl-shaped tris(2,6-diphenylbenzyl)silyl glyoxylate **1** with enol silyl ether under the influence of $BF_3{\cdot}OEt_2$ gave *syn*-aldol product, while the use of $TiCl_4$ afforded *anti*-aldol product with >97% selectivity. © 2002 Elsevier Science Ltd. All rights reserved.

Glyoxylates are extremely useful compounds in organic synthesis, and introduction of various nucleophiles, particularly in an asymmetric manner to prochiral glyoxylates, affords optically active α-hydroxy esters of biological and synthetic importance.[1–3] However, this advantage is seriously diminished by the intrinsic instability of glyoxylates due to the facile hydration and self-polymerization for very reactive aldehyde moiety,[4] and hence fresh distillation of glyoxylates before use is often necessary for their smooth transformation with nucleophiles. Apparently, however, such inconvenience curtails the synthetic potential of the otherwise very useful glyoxylate substrates. In this context, we are interested in the possibility that certain bowl-shaped substituents[5–8] might be highly effective in stabilizing the aldehyde moiety of glyoxylates from the undesired hydration and polymerization without loss of reactivity toward nucleophiles. Here we wish to report the synthesis of bowl-shaped tris(2,6-diphenylbenzyl)silyl glyoxylate **1** (TDS glyoxylate; TDS = tris(2,6-diphenylbenzyl)silyl),[6] by which the synthetic utility of glyoxylates is considerably increased as exemplified by both *syn*- and *anti*-selective aldol reactions, hitherto not observable with ordinary glyoxylates.



Scheme 1. Synthesis of TDS glyoxylate **1**.

Keywords: diastereoselectivity; aldol reaction; glyoxylate; enol silyl ether.

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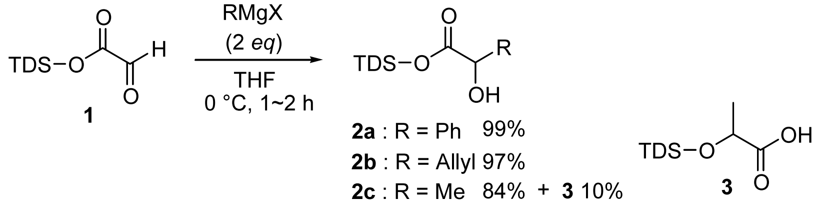


1

2a : R = Ph 99%
2b : R = Allyl 97%
2c : R = Me 84% + **3** 10%

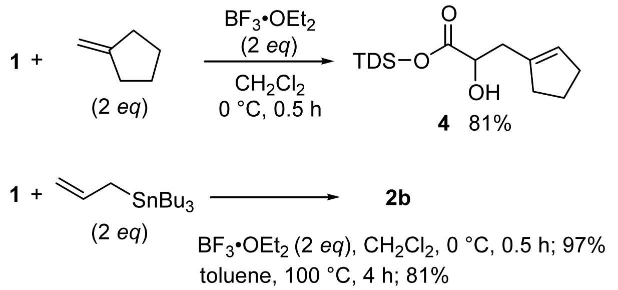
3

Scheme 2. Alkylation of TDS glyoxylate **1** with Grignard reagents.

The requisite TDS glyoxylate **1** can be conveniently synthesized from TDS-Br[6a] in a two-step sequence as shown in Scheme 1. The TDS glyoxylate **1** thus prepared is found to be stable toward self-polymerization and hydration even in the presence of water. This stability is attributable to the existence of an appropriate molecular pocket around the otherwise reactive aldehyde moiety, and this influence is in accord with the unusually high field shift ($\delta = 8.38$) of aldehyde proton in the ^{1}H NMR spectrum [cf. freshly distilled ethyl glyoxylate **7**: $\delta = 9.40$ (CH=O)].[9]

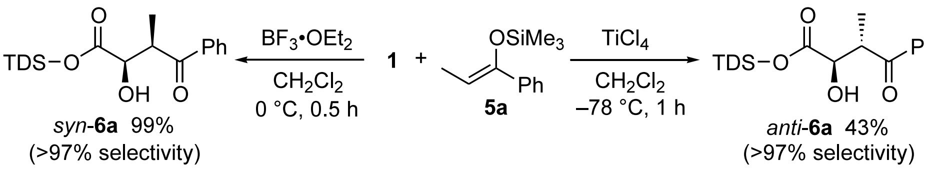
The reactivity of TDS glyoxylate **1** was examined in both ordinary nucleophilic and electrophilic alkylations. For example, treatment of TDS glyoxylate **1** with Grignard reagent (2 equiv. of PhMgBr, allylMgBr, and MeMgI) in THF at 0°C for 1 ∼ 2 h gave rise to the corresponding α-hydroxy esters **2a** ∼ **2c** in high yields (Scheme 2). In the case of methylation, the initially formed α-hydroxy ester partially rearranged to α-siloxy acid **3** in 10% yield. The TDS group of α-hydroxy ester **2a** can be readily cleaved to mandelic acid quantitatively by treatment with HF·Py in THF at 50°C for 5 h with recovery of the TDS group as TDS-F.[6a,10]

$BF_3{\cdot}OEt_2$-promoted ene reaction and allylation of TDS glyoxylate **1** afforded corresponding α-hydroxy esters **4** and **2b**, respectively, in high yields. Moreover, noncatalyzed allylation of TDS glyoxylate **1** with allyltributyltin was also effected at 100°C for 4 h to furnish **2b** in 81% yield.



Another interesting feature of TDS glyoxylate **1** is its applicability to the Lewis acid-promoted diastereoselective aldol reactions with enol silyl ethers or ketene silyl acetals.[11] Indeed, both *syn*- and *anti*-selective aldol reactions of TDS glyoxylate **1** are achievable using two different kinds of ordinary Lewis acids. For example, treatment of TDS glyoxylate **1** with enol silyl ether **5a** (2 equiv.) under the influence of $BF_3{\cdot}OEt_2$ (2 equiv.) at 0°C afforded a *syn*-aldol product (*syn*-**6a**) in 99% yield with virtually complete selectivity. On the other hand, using $TiCl_4$ (2 equiv.) at −78°C a totally opposite *anti*-aldol product (*anti*-**6a**) was obtained in 43% yield (Scheme 3; Table 1, entries 1 and 4).[2c,12] It should be noted, however, that treatment of freshly distilled ethyl glyoxylate **7** with enol silyl ether **5a** under the influence of $BF_3{\cdot}OEt_2$ or $TiCl_4$ afforded the aldol product **8a** with low diastereoselectivity (*syn*/*anti* = 47:53 ∼ 57:43; entries 5 and 6). Other examples including various enol silyl ethers and ketene silyl acetal are listed in Table 1. Several characteristic features of the present diastereoselective aldol reactions follow: (1) In general, high *syn*- and *anti*-selectivity can be observed in the aldol reaction of TDS glyoxylate **1** under the influence of $BF_3{\cdot}OEt_2$ and $TiCl_4$, respectively. However, simple ethyl glyoxylate **7** showed low diastereoselectivity under similar reaction conditions. A similar tendency was also observed with ketene silyl acetal (entries 21 ∼ 24). (2) Both *syn*- and *anti*-selectivity of aldol products **6** derived from TDS glyoxylate **1** were independent of the geometry of enol silyl ethers (entries 7, 8, 11, and 14).[2c,12] (3) *syn*-Selective aldol reactions of TDS glyoxylate **1** with $BF_3{\cdot}OEt_2$ is not sensitive to the reaction temperature (entry 11 versus 12). (4) Among other Lewis acids, Me_2AlCl showed the preferential *syn*-selectivity (entries 2 and 13), while only low diastereoselectivity was observed in the case of $SnCl_4$ (entry 3).

Since both *syn*- and *anti*-selectivities of aldol products **6** can be achieved irrespective of the geometry of enol silyl ethers, the present reactions are most likely to



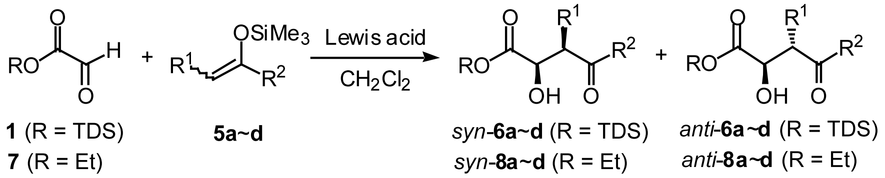
syn-**6a** 99%
(>97% selectivity)

5a

anti-**6a** 43%
(>97% selectivity)

Scheme 3. Diastereoselective aldol reactions of glyoxylate **1** under the influence of $BF_3{\cdot}OEt_2$ or $TiCl_4$.

Table 1. Diastereoselective aldol reactions of glyoxylates[a]

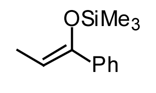


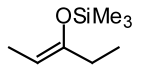
Entry	Glyoxylate	Silyl ether	Lewis acid	Conditions (°C, h)	Yield (%)[b] (*syn*/*anti*)[c]
1	**1**	**5a**	$BF_3 \cdot OEt_2$	0, 0.5	99 (>97:<3)
2			Me_2AlCl	−78, 1	84 (>97:<3)
3			$SnCl_4$	−78, 1	92 (53:47)
4			$TiCl_4$	−78, 1	43 (<3:>97)
5	**7**		$BF_3 \cdot OEt_2$	0, 0.5	84 (47:53)
6			$TiCl_4$	−78, 1	28 (57:43)
7	**1**	*Z*-**5b**	$BF_3 \cdot OEt_2$	0, 0.5	88 (94:6)
8			$TiCl_4$	−78, 1	80 (3:97)
9	**7**		$BF_3 \cdot OEt_2$	0, 0.5	40 (53:47)
10			$TiCl_4$	−78, 1	55 (45:55)
11	**1**	*E*-**5b**	$BF_3 \cdot OEt_2$	0, 0.5	99 (77:23)
12			$BF_3 \cdot OEt_2$	−78, 5	55 (75:25)
13			Me_2AlCl	−78, 1	74 (67:33)
14			$TiCl_4$	−78, 1	74 (5:95)
15	**7**		$BF_3 \cdot OEt_2$	0, 0.5	49 (49:51)
16			$TiCl_4$	−78, 1	57 (50:50)
17	**1**	**5c**	$BF_3 \cdot OEt_2$	0, 0.5	99 (72:28)
18			$TiCl_4$	−78, 1	82 (10:90)
19	**7**		$BF_3 \cdot OEt_2$	0, 0.5	65 (44:56)
20			$TiCl_4$	−78, 1	62 (50:50)
21	**1**	**5d**	$BF_3 \cdot OEt_2$	0, 0.5	97 (90:10)
22			$TiCl_4$	−78, 1	98 (7:93)
23	**7**		$BF_3 \cdot OEt_2$	0, 0.5	58 (47:53)
24			$TiCl_4$	−78, 1	22 (44:56)

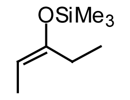
[a] The aldol reaction was carried out with silyl ether (2 equiv.) in the presence of Lewis acid (2 equiv.) in CH_2Cl_2 under the given reaction conditions.

[b] Isolated yield.

[c] Determined by ^{1}H NMR analysis.


(*Z*/*E* = >97 : <3)
5a


(*Z*/*E* = 86 : 14)
Z-**5b**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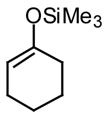
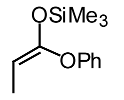
E-**5b**


5c


(*Z*/*E* = 4 : 96)
5d

proceed via acyclic transition states.[13] The *syn*-selectivity under the influence of $BF_3 \cdot OEt_2$ is explained by the steric repulsion between bulky siloxy moiety of TDS glyoxylate **1** and R^1 of enol silyl ethers (Scheme 4, A>B). On the other hand, the *anti*-selectivity using $TiCl_4$ is ascribed to the steric interaction between $TiCl_4$ and R^1 of enol silyl ethers (C<D).[14] Such an *anti*-selective aldol reaction, which is independent of the geometry of enol silyl ethers, is relatively rare.[11b,15]

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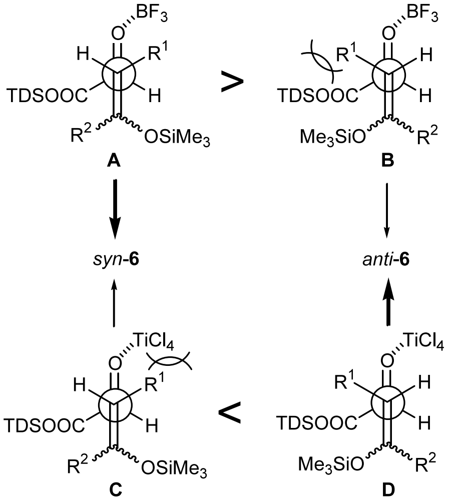

Scheme 4. Assumed transition states for *syn*- and *anti*-selectivity.

References

1. Reviews of glyoxylates in organic synthesis: (a) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639; (b) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117; (c) Jurczak, J.; Bauer, T. *Pure Appl. Chem.* **2000**, *72*, 1589.
2. (a) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988; (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; (c) Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 4231.
3. Review of α-hydroxy carboxylic acids: Gröger, H. *Adv. Synth. Catal.* **2001**, *343*, 547.
4. Kelly, T. R.; Schemidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.
5. Reviews of bowl-shaped compounds: (a) Goto, K.; Okazaki, R. *Liebigs Ann./Recueil* **1997**, 2393; (b) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.
6. Chemistry of bowl-shaped tris(2,6-diphenylbenzyl)silyl group: (a) Iwasaki, A.; Kondo, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 10238; (b) Shirakawa, S.; Komatsu, N.; Iwasaki, A.; Maruoka, K. *Synlett* **2002**, 577; (c) Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2002**, *43*, 1469.
7. For related study on the similar bowl-shaped tris(2,6-diphenylbenzyl)tin hydride and tris(2,6-diphenylbenzyl)amine, see: (a) Sasaki, K.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 411; (b) Sasaki, K.; Komatsu, N.; Shirakawa, S.; Maruoka, K. *Synlett* **2002**, 575; (c) Naiki, M.; Shirakawa, S.; Kon-i, K.; Kondo, Y.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 5467.
8. Another example of bowl-shaped silyl compounds with shallow cavity: Goto, K.; Okumura, T.; Kawashima, T. *Chem. Lett.* **2001**, 1258.
9. Attempted synthesis of triisopropylsilyl glyoxylate by ozonolysis of triisopropylsilyl acrylate resulted in formation of polymeric products.
10. Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744.
11. Diastereoselective aldol reactions of glyoxylates: (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039; (b) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.
12. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p. 111.
13. (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, p. 997; (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.
14. Addition of aldehydes with $TiCl_4$ is reported to give 2:1 coordination complexes, in which the formal bulk of $TiCl_4$ is increased due to its octahedral coordination. See: (a) Urabe, H.; Sato F. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2; p. 653; (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256; (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747; (d) Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Pizzol, C. *Chem. Ber.* **1996**, *129*, 1361.
15. (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447; (b) Yamashita, Y.; Ishitani, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.