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Super Silyl Stereo-Directing Groups for Complete 1,5-Syn and -Anti Stereoselectivities in the Aldol Reactions of β -Siloxy Methyl Ketones with Aldehydes

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Polyketides are an important class of natural products, and the 1,3-polyol motif is commonly found in these biologically significant compounds.¹ Undoubtedly, the asymmetric aldol reaction provides a straightforward route for the stereoselective construction of these required polyol subunits. We recently introduced a cascade Mukaiyama aldol reaction, based on super silyl and super Brønsted acid chemistry, which gave the required polyol-carbonyls stereoselectively in a single step (Scheme 1A and 1B).^{2,3} To upgrade the cascade process for even broader utility, such as rapid construction of polyketide frameworks, we here focus on 1,5-stereoselective aldol reactions directly using our cascade products, which represent a series of two consecutive aldol reactions of a central ketone with two polyol-aldehydes (Scheme 1C).^{4,5}

General methodologies for high 1,5-stereoselection in the aldol reaction of methyl ketones have not yet been established, because the reaction site is far from the chiral center of the substrate as compared with 1,2- or 1,3-inductions. Nonetheless, several methods for 1,5-*anti* asymmetric induction in aldol reactions have been disclosed.⁶ The most commonly used method of 1,5-*anti* induction is the boron-mediated aldol reaction of β -alkoxy methyl ketones with aldehydes. Unfortunately, switching the protecting group from β -alkoxy to a siloxy group led to significantly lower diastereoselectivities, with a few exceptions.⁷ Thus, the method cannot be used directly on the product of Mukaiyama aldol reactions and requires extra deprotection and protection steps. To obtain 1,5-*syn* stereoselectivity in aldol reactions using methyl ketones is even more difficult.⁸ Synthetic methods to achieve 1,5-asymmetric induction in the context of asymmetric synthesis have been reported by both Denmark^{8a–c} and Dias.^{8d,e} However, a general diastereoselective approach to 1,5-*syn* induction is still challenging. Herein we report new methods for both high 1,5-*syn* and -*anti* induction in the aldol reaction of β -siloxy methyl ketones with aldehydes using substrate control.

To examine whether the use of bulky β -super siloxy groups could lead to high 1,5-stereoselection in the aldol reaction, compounds **1a** and **2a** were prepared using our reported methodology.² Simple treatment of the lithium enolate of **1a** with pivalaldehyde in THF at -78°C gave **4a** with low selectivity (Table 1, entry 1). The use of non-coordinating solvents, such as CH_2Cl_2 and toluene gave low selectivities (entries 2 and 3). Gratifyingly, the use of DMF as the solvent gave *syn*-**4a** in 94% yield with good selectivity (entry 4). Finally, when the TMS-type super silyl group was changed to the TES-type super silyl group, [*tris*(triethylsilyl)silyl]

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Supporting Information Available: Experimental procedures, characterization of compounds **1a–d**, **1a–d**, **2a–d**, *syn*-**4a**, *anti*-**4a–m**, *anti*-**5a**, *syn*-**5a–m**, **7–13**, and including these ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

⁹, the diastereoselectivity was increased to 96:4 (entry 5). As anticipated, the use of **3a**, with a much smaller TBS protecting group gave **6a** in low selectivity (entry 6). Apparently, the super silyl group plays an important role in achieving high selectivity due to its extreme steric bulk as compared to other silyl groups.^{2a}

Since metallocyclic and acyclic transition states frequently give the opposite stereoselectivity in the aldol reactions,¹⁰ we evaluated the possibility of a 1,5-*anti* aldol reaction with **1a** under acidic conditions. Thus, the aldol reactions of the silyl enol ethers of **1a** and pivalaldehyde, catalyzed by Tf₂NH, were investigated (Table 1, entries 7–12). The use of the trimethylsilyl enol ether of **1a** in CH₂Cl₂ gave *anti*-**4a** in 82% yield with high selectivity (95:5, entry 7). The selectivity was decreased when the triethylsilyl enol ether of **1a** was used (entry 8). The use of hexane caused a decrease in the yield of **4a**, whereas the use of toluene gave an 82% yield of *anti*-**4a** almost exclusively (97:3, entries 9 and 10). When the TES-type super silyl derivative **2a** was tested, selectivity was increased to 98:2 with a slight decrease in yield (entry 11). As anticipated, the use of TBS protected **3a** gave the product **6a** with a very low selectivity (entry 12).¹¹

Plausible transition-state structures for the 1,5-*syn* and 1,5-*anti* selectivities are shown in Figure 1. Both transition states should adopt conformation **A**, because it does not suffer the unfavorable steric interaction between the R¹ group and the olefin of the enolate that is present in conformation **B**. In the case of the lithium mediated aldol reaction, *syn* selectivity can be attributed to the unfavorable 1,3-diaxial interactions found in transition-state **D**, which are absent in transition-state **C**. A bulkier coordinating solvent such as THF destabilizes conformation **A**, due to the repulsion between R¹ and the coordinated solvent molecules, leading to lower *syn* selectivity. For the case of the acid-catalyzed aldol reaction, *anti* selectivity is observed because transition-state **E** has less interaction between the R² group and the methylene group in transition-state **F**. Switching to a bulkier silyl group of silyl enol ether destabilizes conformation **A**, due to the repulsion between the R¹ group and the siloxy group, leading to lower *anti* selectivity.

Under the optimized reaction conditions, the 1,5-*syn* selective aldol reaction was achieved using various aldehydes and methyl ketones, the results of which are summarized in Table 2. The reactions of **2a** with various aliphatic aldehydes gave *syn*-**5a–5d** with high diastereoselectivities (entries 1–4). The aldol reactions of **2a** with aromatic and conjugated aldehydes gave *syn*-**5e–5g** with slightly lower diastereoselectivities (entries 5–7). Methyl ketones bearing various β-alkyl substituents (**2b–2d**) produced *syn*-**5h–5m** in high diastereoselectivities (entries 8–13). Thus, the 1,5-*syn* aldol reaction using TES-type supersilyl group proved to be rather general in scope.

Furthermore, the substrate scope for the 1,5-*anti* selective aldol reaction was also investigated (Table 3). The aldol reactions of **1a** with various aldehydes gave *anti*-**4a–4g** with high diastereoselectivities (entries 1–7), and methyl ketones bearing several β-alkyl substituents (**1b–1d**) also gave *anti*-**4h–4m** without any exceptions (entries 8–13). Thus, the *anti* selective acidic aldol process also proved to be very general.

Next, we investigated the conversion of *anti*- and *syn*-**5a** to 1,3,5-triol motifs (Scheme 2). *Syn/anti*-1,3,5-triol **7** was obtained by the simple NaBH₄ reduction of *anti*-**5a** with excellent selectivity (Scheme 2A).¹² *Syn/syn*-1,3,5-triol **7** was also obtained by the NaBH₄ reduction of *syn*-**5a** with high selectivity (Scheme 2B). These selectivities depend heavily on the *tris* (triethylsilyl)siloxy group due to its overwhelming steric hindrance. It should be noted that the TES-type super silyl, *tris*(triethylsilyl)siloxy group was also cleanly cleaved in MeOH/CH₂Cl₂ upon irradiation with UV light.¹³ *Anti/anti*-1,3,5-triol **8** was obtained by

intramolecular hydrosilylation reduction catalyzed by scandium triflate and desilylation sequence of *syn*-**5a** (Scheme 2C).^{14–16}

Finally, the double-stereodifferentiating aldol reactions of these enolates were examined, giving us a unique opportunity to study the absolute stereocontrol of the 1,5- versus 1,2-inductions (Scheme 3). The aldol reaction of the lithium enolate of **9**¹⁷ with aldehyde **11**¹⁷ in DMF gave **12** in high selectivity (Scheme 3A). However, the reaction of the lithium enolate of **9** with *ent*-**11** gave **13** in low selectivity (Scheme 3B). On the other hand, the aldol reactions of **10** with **11** and *ent*-**11** gave **12** and **13**, respectively, both with high selectivity (Scheme 3C and 3D). Thus, under acidic conditions, 1,2-induction predominates in both cases while metalloenolate conditions gave 1,5-induction competing with the 1,2-process (Scheme 3B).

In summary, we have developed (1) 1,5-*syn* selective aldol reactions of lithium enolates of β -super siloxy methyl ketones and aldehydes in DMF; (2) 1,5-*anti* selective aldol reactions of the trimethylsilyl enol ethers of methyl ketones with aldehydes catalyzed by Tf₂NH in toluene; (3) a stereoselective synthesis of 1,3,5-*syn/syn* or *anti/anti* triol derivatives **7** from 1,5-*syn* products **5a**; and (4) a stereoselective synthesis of 1,3,5-*syn/anti* triol derivative **7** from 1,5-*anti* product **5a**. These methods are advantageous in 1,5-stereoiduction, which can be achieved from the same starting material and all 1,3,5-triol stereoisomers can be easily prepared. Applications of this methodology in the synthesis of long chain complex polyketides are currently under investigation (Scheme 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (16). The use of B(C₆F₅)₃ as Lewis acid instead of Sc(OTf)₃ gave 1,3,5-*syn/syn* product as single isomer. The relative configuration of product **5a**, **7** and **8** were determined by the NMR spectra of these related compounds. See Supporting Information for full details.
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Figure 1.
Plausible transition-states for 1,5-*syn* and 1,5-*anti* inductions.

Scheme 1.

Aldol reactions utilizing 1,3- and 1,5-stereoinduction.

Scheme 2.
Syntheses of 1,3,5-triols.

Scheme 3.
Double stereodifferentiating aldol reactions.

Table 1

Optimization of aldol reaction of **1a–3a** with pivalaldehyde.

entry	substrate	enolization reagent	T (°C)	solvent	yield (%) ^a	syn:anti ^b
1	1a	LiHMDS	-78	THF	89	40:60
2	1a	LiHMDS	-60	CH ₂ Cl ₂	50	60:40
3	1a	LiHMDS	-60	toluene	70	60:40
4	1a	LiHMDS	-60	DMF	94	87:13
5	2a	LiHMDS	-60	DMF	82	96:4
6	3a	LiHMDS	-60	DMF	69	66:34
7	1a	TMSOTf/Et ₃ N ^c	-78	CH ₂ Cl ₂	82	5:95
8	1a	TESOTf/Et ₃ N ^c	-78	CH ₂ Cl ₂	65	15:85
9	1a	TMSOTf/Et ₃ N ^c	-78	hexane	72	15:85
10	1a	TMSOTf/Et ₃ N ^c	-78	toluene	82	3:97
11	2a	TMSOTf/Et ₃ N ^c	-78	toluene	79	2:98
12	3a	TMSOTf/Et ₃ N ^c	-78	toluene	78	45:55

^a Isolated yields.

^b Ratios determined by ¹H NMR or GC analysis.

^c After isolation of silyl enol ether of **1–3a**, the aldol reaction was carried out by using 0.2 mol% Tf₂NH in the indicated solvent.

Table 2

Substrate scope of 1,5-*syn* aldol reactions with **2a–2d**.

entry	R ¹	R ²	product (yield) ^a	syn:anti ^b
1	<i>t</i> -Bu (2a)	<i>t</i> -Bu	5a (82)	96:4
2	<i>t</i> -Bu (2a)	<i>i</i> -Pr	5b (82)	95:5
3	<i>t</i> -Bu (2a)	<i>c</i> -Hex	5c (77)	96:4
4	<i>t</i> -Bu (2a)	<i>n</i> -Hept	5d (70)	93:7
5	<i>t</i> -Bu (2a)	4-MeO-Ph	5e (72)	89:11
6	<i>t</i> -Bu (2a)	4-NO ₂ -Ph	5f (70)	88:12
7	<i>t</i> -Bu (2a)	PhCH=CH (E)	5g (83)	85:15
8	<i>i</i> -Pr (2b)	<i>t</i> -Bu	5h (84)	96:4
9	<i>i</i> -Pr (2b)	<i>c</i> -Hex	5i (80)	95:5
10	<i>c</i> -Hex (2c)	<i>t</i> -Bu	5j (84)	97:3
11	<i>c</i> -Hex (2c)	<i>c</i> -Hex	5k (82)	97:3
12	<i>n</i> -Hept (2d)	<i>t</i> -Bu	5l (85)	93:7
13	<i>n</i> -Hept (2d)	<i>c</i> -Hex	5m (80)	92:8

^a Isolated yields (%).^b Ratios determined by crude ¹H NMR.

Table 3Substrate scope of 1,5-*anti* aldol reactions with **1a**–**1d**.

entry	R^1	R^2	product (yield) ^a	anti:syn ^b
1	<i>t</i> -Bu (1a)	<i>t</i> -Bu	4a (82)	97:3
2	<i>t</i> -Bu (1a)	<i>i</i> -Pr	4b (87)	95:5
3	<i>t</i> -Bu (1a)	<i>c</i> -Hex	4c (80)	97:3
4	<i>t</i> -Bu (1a)	<i>n</i> -Hept	4d (91)	95:5
5	<i>t</i> -Bu (1a)	4-MeO-Ph	4e (85)	97:3
6	<i>t</i> -Bu (1a)	4-NO ₂ -Ph	4f (92)	95:5
7	<i>t</i> -Bu (1a)	PhCH=CH (E)	4g (83)	98:2
8	<i>i</i> -Pr (1b)	<i>t</i> -Bu	4h (90)	98:2
9	<i>i</i> -Pr (1b)	<i>c</i> -Hex	4i (87)	97:3
10	<i>c</i> -Hex (1c)	<i>t</i> -Bu	4j (77)	95:5
11	<i>c</i> -Hex (1c)	<i>c</i> -Hex	4k (74)	97:3
12	<i>n</i> -Hept (1d)	<i>t</i> -Bu	4l (71)	94:6
13	<i>n</i> -Hept (1d)	<i>c</i> -Hex	4m (78)	97:3

^a Isolated yields (%).^b Ratios determined by crude 1H NMR.