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Organocatalyzed Direct Aldol Reaction of Silyl Glyoxylates for the Synthesis of α-Hydroxysilanes

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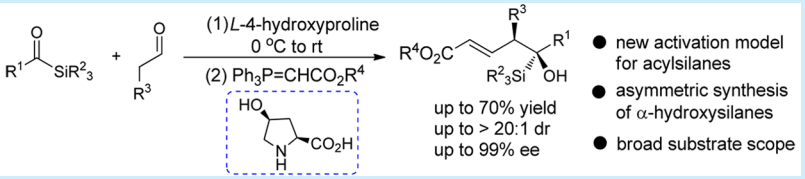
Supporting Information



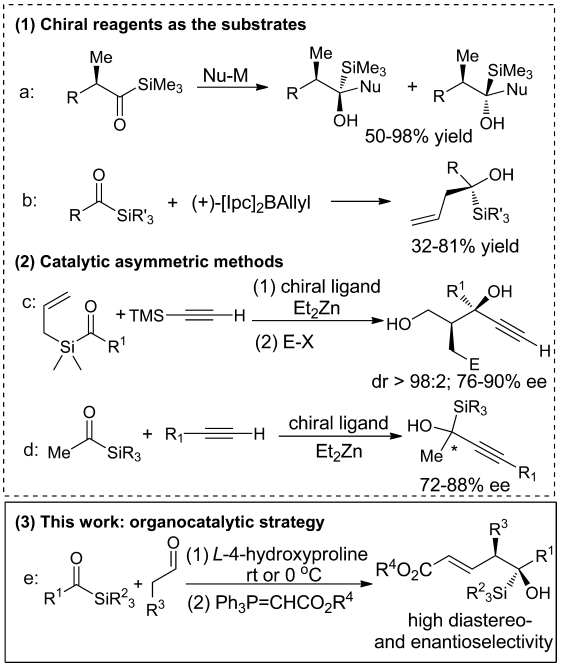
ABSTRACT: A novel organocatalyzed direct aldol reaction of aldehydes to silyl glyoxylates is disclosed. This method provides an efficient route to α-hydroxysilanes with excellent enantioselectivities (up to 99% ee) and high diastereoselectivities (up to >20:1 dr). In the new activation model of silyl glyoxylates, the hydrogen bond is critical to the reaction. A carbonyl group directly attached to silicon in acylsilanes could be activated by coordination to the proton of hydroxyl and carboxylic acid via a hydrogen bond. Moreover, commercially available *cis*-L-4-hydroxyproline is an ideal organocatalyst for activating both aldehydes and acylsilanes.

Because of their structural uniqueness,[1] α-hydroxysilanes have attracted considerable attention for both their preparation[2] and synthetic utilities,[3] and the development of efficient methods for their preparation is in high demand.

To date, there are two main strategies for the synthesis of enantiopure α-hydroxysilane. The first is nucleophilic addition with chiral reagent as the substrate. Chiral acylsilanes[4] or chiral nucleophiles[5] are often used in this strategy. For example, in 1988, Ohno and co-workers[4e] reported a nucleophilic addition of chiral acylsilane to synthesize α-hydroxysilanes (Scheme 1a). In contrast, a complementary method introduced by Buynak,[5b] utilizes an asymmetric allylboration of acylsilanes with stoichiometric amounts of allyldiisopinocampheylborane as chiral nucleophile (Scheme 1b). However, the enantioselectivity achieved is highly substrate dependent. In the second, alternative synthetic method, the catalytic asymmetric method is considered to be the most appealing.[6] For example, both Marek[6b,c] and Chan[6h] applied zinc-catalyzed asymmetric alkynylation of acylsilanes to the synthesis of optically active α-hydroxysilanes, providing the corresponding products in moderate to high enantioselectivities (Scheme 1c,d). The efficient methodology with broad substrate scope in the catalytic asymmetric synthesis of α-hydroxysilanes remains rare. Thus, the development of a catalytic asymmetric method for the synthesis of optically active α-hydroxysilanes is highly desirable.

On the other hand, organocatalytic asymmetric aldol reactions have emerged as an attractive tool for the synthesis of optically active compounds.[7] In connection with our focus on investigating the new synthetic methods,[8] we recently questioned whether it might be possible to direct activate acylsilanes through organocatalysis because acylsilanes can be considered as an aldehyde equivalent.[9] From a synthetic point of view, the direct activation of unactivated acylsilanes is great challenge for organocatalytic asymmetric aldol reaction.[1a] To

Scheme 1. Representative Activation Models for Acylsilanes



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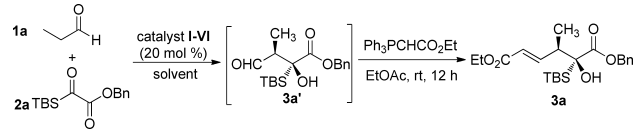
address this issue, a new activation model for acylsilanes is required. In this context, a novel organocatalyzed direct aldol reaction of acylsilanes and aldehydes was developed (Scheme 1e). We envisioned that the carbonyl group directly attached to silicon in acylsilanes could be activated by coordination to the proton of hydroxyl and carboxylic acid via a hydrogen bond.[10] Meanwhile, aldehyde can serve as a nucleophile. In addition, inexpensive and commercially available *cis*-L-4-hydroxyproline is an ideal organocatalyst for activating both aldehydes and acylsilanes. Herein, we report an organocatalytic asymmetric aldol reaction of aldehydes with silyl glyoxylates, affording α-hydroxysilanes products in excellent diastereo- and enantioselectivities (up to 99% ee and up to >20:1 dr). To our knowledge, this new activation model for acylsilanes has not been reported.

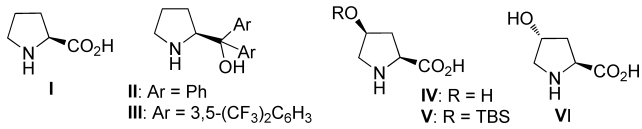
Aiming to realize the new aldol reaction for enantioselective synthesis of α-hydroxysilanes, we first examined the aldol reaction[11] of propanal **1a** with silyl glyoxylate **2a**.[1b] In the presence of proline (20 mol %) as catalyst, the aldol reaction proceeded well in DMF, and the corresponding aldol product **3a** was obtained in 52% yield with high diastereoselectivity (20:1 dr) and moderate enantioselectivity (77% ee) (Table 1, entry 1). Encouraged by this result, we further screened other proline's derivatives **II**–**VI** as chiral catalysts in the reaction. As shown in Table 1, the catalytic activity varies significantly with different catalyst structures. No desired product was obtained when **II** and **III** were used as the catalysts (Table 1, entries 2 and 3), revealing that the acidic proton is critical to activate the silyl glyoxylate via H-bonding. Notably, L-4-hydroxyproline (**IV**) bearing an extra hydroxy group in the C4-position was found to enhance enantioselectivity of the model reaction dramatically, generating product **3a** in 94% ee (Table 1, entry 4). Further investigation showed that catalyst **V**, in which the OH group at the C4-position of catalyst **IV** was protected by TBS, was applied to the reaction, only a trace amount of aldol product was observed (Table 1, entry 5). Compared to *cis*-L-4-hydroxyproline, the yield was slight decreased with *trans*-L-4-hydroxyproline **VI** as catalyst (Table 1, entry 6). When the reaction temperature was lowered to 0 °C, product **3a** was obtained in slightly lowered yield with the same enantioselectivity (Table 1, entry 7). It was found that a decreased amount of catalyst led to lower yields of product with lower diastereoselectivity and enantioselectivity as the background reaction (Table 1, entries 8 and 9). In addition, other solvents, such as CH_3CN, toluene, CH_2Cl_2, and THF were also examined, and no desired product was isolated (Table 1, entries 10–13), indicating that the polar solvent of DMF is optimal in this process.

With the optimal reaction conditions, we next investigated the substrate scope for the asymmetric aldol reaction. A series of silyl glyoxylates were synthesized[12] and subjected to the reaction. In general, silyl glyoxylates bearing different ester group were well tolerated. As summarized in Scheme 2, all of the halogen atom substituted substrates (**2b**–**e**) were well tolerated and gave the corresponding α-hydroxysilane products (**3b**–**e**) in excellent enantioselectivities and high diastereoselectivities. It is noteworthy that silyl glyoxylate with a strong electron-withdrawing ester group (**2f**) afforded the desired product **3f** with low diastereoselectivity (1:1 dr) and high enantioselectivities (84/99% ee). Reaction with a bulky 2-naphthyl ester group on the silyl glyoxylate also gave the corresponding product **3g** with 6:1dr and 65/96% ee.

Table 1. Optimization of the Reaction Conditions[a]

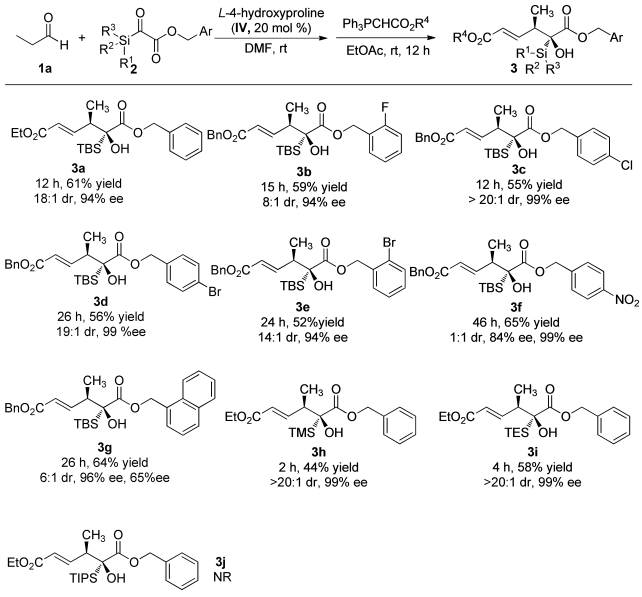


entry	catalyst	solvent	time	yield[b] (%)	dr[c]	ee[d](%)
1	I	DMF	27	52	20:1	77
2	II	DMF	48	trace	ND	ND
3	III	DMF	48	trace	ND	ND
4	IV	DMF	12	64	>20:1	94
5	V	DMF	14	trace	ND	ND
6	VI	DMF	14	62	>20:1	94
7[e]	IV	DMF	20	56	>20:1	94
8[f]	IV	DMF	36	61	18:1	92
9[g]	IV	DMF	42	28	19:1	87
10	IV	CH_3CN	48	trace	ND	ND
11	IV	toluene	48	NR	ND	ND
12	IV	CH_2Cl_2	48	trace	ND	ND
13	IV	THF	24	trace	ND	ND



[a]Reactions were performed with 0.20 mmol of **1a**, 0.10 mmol of **2a**, and 20 mol % of catalyst (**I**–**VI**) in 0.5 mL of solvent and stirred for the indicated time at rt. [b]Isolated yield after purification by column chromatography. [c]Determined by ^1H NMR analysis of crude mixture. [d]Determined by chiral HPLC analysis. [e]The reaction was carried out at 0 °C. [f]10 mol % of catalyst **IV** was used. [g]5 mol % of catalyst **IV** was used. NR = no reaction. ND = not detected.

Scheme 2. Enantioselective Direct Aldol reaction of Propanal (1a) to Silyl Glyoxylates (2)[a]



[a]Reactions were performed with 0.20 mmol of **1a**, 0.10 mmol of **2**, and 20 mol % of catalyst IV in 0.5 mL of DMF at rt. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

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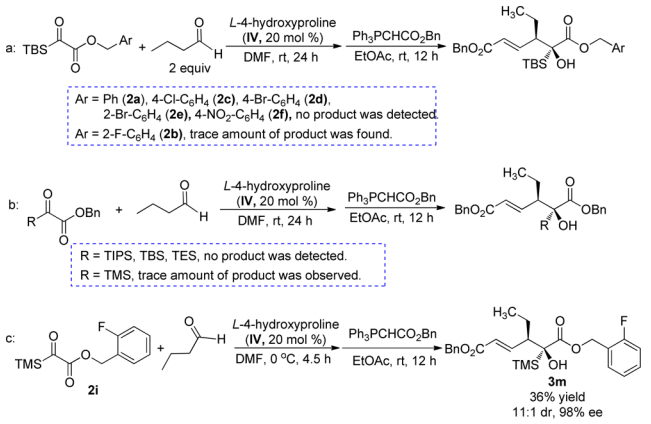
Furthermore, excellent enantioselectivities (99% ee) and high diastereoselectivities (>20:1 dr) were successfully obtained by the introduction of TMS or TES instead of silyl glyoxylates (**3h** and **3i**). In contrast, the silyl glyoxylate bearing a bulky TIPS group did not provide the desired product **3j**. Unfortunately, we failed to obtain the desired product when the reaction of **2a** with butanal was carried under the optimized reaction conditions. To further expand the scope of this reaction, we re-examined the reactivity of silyl glyoxylates. Interestingly, a trace amount of the product was observed when the substrate (**2b**) with a fluorine atom on the *ortho*-position of benzyl ester moiety reacted with butanal (Scheme 3a). The reactivity of silyl

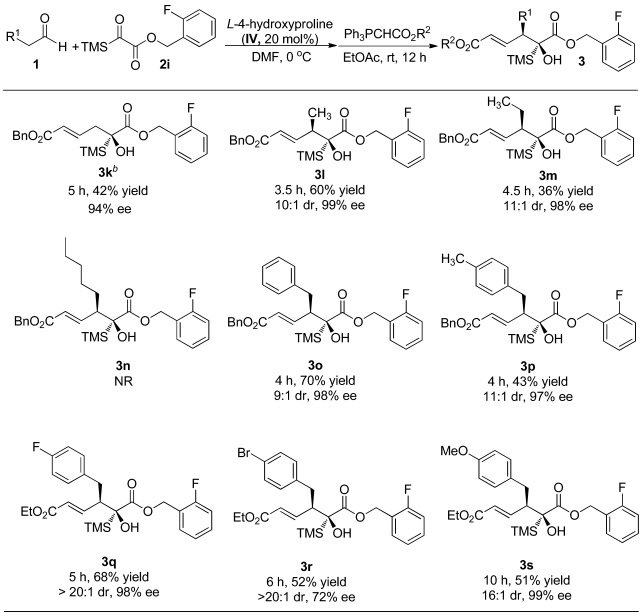
Scheme 3. Representative Activation Models for Acylsilanes



glyoxylates with different silicon moieties was also investigated. Compared to the large size of silicon moieties including TIPS, TBS, and TES, the small size of TMS with less steric hindrance gave a trace amount of product (Scheme 3b). We considered that both the substituent effect of the ester group and the steric effect of the silicon moiety would be the key factor in this aldol reaction. Consequently, a new silyl glyoxylate **2i** was designed and synthesized, and it should have sufficient reactivity through the coordination effect with catalyst via hydrogen bonding. To our delight, the reaction of butanal and silyl glyoxylate **2i** with *o*-fluoro on the benzene ring of benzyl ester proceed well in DMF at 0 °C, affording the desired product in excellent enantioselectivity (98% ee) and high diastereoselectivity (11:1 dr) (Scheme 3c). Accordingly, the silyl glyoxylate **2i** was employed as the substrate to further survey the reaction.

In the course of further investigation of the reaction scope, the results are shown in Scheme 4. It was found that the high reactivity of acetaldehyde as a nucleophile can be successfully used in the reaction, generating product **3k** in excellent enantioselectivity (95% ee). α-Alkyl-substituted acetaldehydes, such as propanal and butanal, were examined, providing the corresponding products in excellent enantioselectivities (95% for **3l**, and 98% for **3m**). Heptanal was also employed as the nucleophile, but no desired product (**3n**) was obtained. Notably, when a phenyl group was introduced into the aldehyde substrate, the reaction also gave the desired product (**3o**) in high enantioselectivity (98% ee). Next, a variety of substituents on the phenyl rings were subjected to the reaction with **2i**. When the reactions of **2i** and the nucleophile aldehydes with *p*-Me, *p*-F, and *p*-MeO attached to the phenyl rings, the corresponding products were obtained in excellent enantioselectivities high diastereoselectivities (97% ee and 11:1 dr for **3p**, 98% ee and >20:1 dr for **3q**, 99% ee and 16:1 dr for **3s**).

Scheme 4. Enantioselective Direct Aldol Reaction of Silyl Glyoxylates 2i with Various Aldehydes[a]

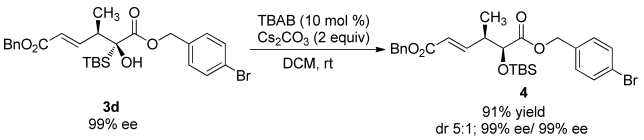


[a]Reactions were performed with 0.20 mmol of **1a**, 0.10 mmol of **2i**, and 20 mol % of catalyst IV in 0.5 mL of DMF at 0 °C. [b]4 equiv of acetaldehyde was used.

Aldehyde bearing a Br provided the product (**3r**) in >20:1 dr and 72% ee. We also examined ketone including cyclopentanone, cyclohexanone, acetophenone, and acetone as the nucleophile, but no desired products were detected.

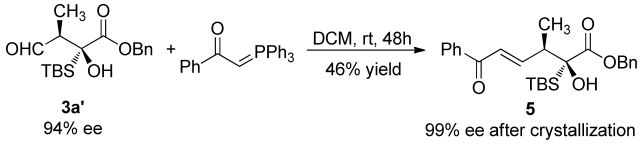
To demonstrate the synthetic utility of aldol products, [1,2]-Brook rearrangement of **3d** was performed in DCM at room temperature by using 10 mol % of TBAB and 2 equiv of Cs_2CO_3, and the corresponding product **4** was obtained in high yield (91% yield) and excellent enantioselectivities (99/99% ee), but the dr value decreased to 5:1 (Scheme 5).

Scheme 5. Brook Rearrangement of 3d to 4



To determine the absolute configuration of the products, the chiral products **3a′** was easily converted to compound **5** in 46% yield (Scheme 6). The X-ray structural analysis indicates that the absolute configuration of **5** is (2*R*,3*R*), and therefore, the absolute configuration of the **3a** could be concluded to be (4*R*,5*R*). Based on the absolute configuration of the product **3a**, we proposed a possible transition-state model for the organocatalyzed addition. As shown in Figure 1, catalyst **IV**

Scheme 6. Transformation of 3a′ to 5



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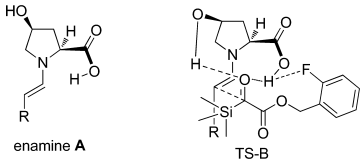

Figure 1. Transition-state models.

reacts with aldehyde to generate enamine A. Subsequently, enamine A reacts with silyl glyoxylate through the transition state B. The carbonyl group of silyl glyoxylate can be activated by coordination to the proton of hydroxyl and carboxylic acid via hydrogen bond. This interaction will be stronger in the presence of an F atom[13] on the ester group in the transition state B. Therefore, the hydrogen bond is critical to this reaction.

In summary, a novel activation model for acylsilanes was developed and realized by organocatalyzed direct aldol reaction of silyl glyoxylates and aldehydes. This method enables efficient synthesis of enantiopure α-hydroxysilanes in up to 99% ee and >20:1 dr. There are several features in the reaction: (1) commercially available *cis*-L-4-hydroxyproline is an ideal organocatalyst for activating both aldehydes and acylsilanes; (2) the hydrogen bond is critical to this reaction, and the carbonyl group directly attached to silicon in acylsilanes could be activated by the coordination effect of protons of hydroxyl and carboxylic acid via hydrogen bond; (3) silyl glyoxylate **2i** with *o*-F on the benzene ring of benzyl ester was employed to expand the reaction scope. Further studies of new reaction of acylsilanes are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00811.

Full experimental details and characterization data for all products(PDF)

X-ray data for compound **5** (CIF)

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Notes

The authors declare no competing financial interest.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1536128).

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