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Hydrogen-Bond-Assisted Sequential Reaction of Silyl Glyoxylates: Stereoselective Synthesis of Silyl Enol Ethers

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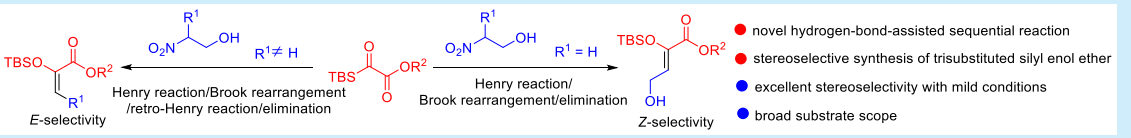
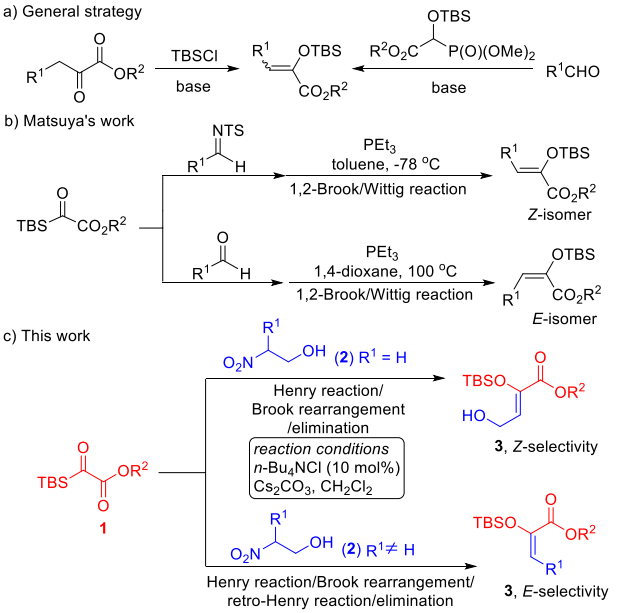


ABSTRACT: A novel hydrogen-bond-assisted sequential reaction of silyl glyoxylates is described. This method provides an efficient strategy for the synthesis of silyl enol ethers with high selectivity. In these transformations, hydrogen bonds from 2-nitroethanol and its derivatives are critical to the stereochemical outcome. Both *E*- and *Z*-isomers are achieved via Henry reaction/Brook rearrangement/elimination and Henry reaction/Brook rearrangement/retro-Henry reaction/elimination processes, respectively (up to 99:1 *Z*-selectivity, and 9.2:1 *E*-selectivity).

As valuable intermediates, silyl enol ethers have been widely used in organic synthesis, especially in Mukaiyama-type aldol reactions and Mannich-type reactions.[1] Among various types of silyl enol ethers, trisubstituted silyl enol ethers bearing an electron-withdrawing group are often utilized as prochiral substrates in several valuable reactions, generating products with a new stereogenic center, and the diastereoselectivity often arises from the geometry of trisubstituted silyl enol ethers.[2] The stereocontrolled synthesis of structurally well-defined silyl enol ethers is highly required in these reactions.

To date, many synthetic methods have been well developed from a series of starting materials. Generally, the base-induced silylation of ketoesters[3] and the Horner−Wadsworth−Emmons (HWE) reaction of aldehydes[2g,4] can be conveniently used for the preparation of trisubstituted silyl enol ethers (Scheme 1a). However, the high *E*/*Z* geometry of trisubstituted silyl enol ethers is hampered by many factors, such as reaction conditions and substituents. Considering the limitations of typical methods, Matsuya and co-workers reported a novel sequential 1,2-Brook/Wittig reaction of silyl glyoxylates[5] for the preparation of silyl enol ethers (Scheme 1b). In this method, both geometric isomers of silyl enol ethers were produced using aldehydes (*E*-selectivity) and tosylimines (*Z*-selectivity) as a Wittig electrophile. Despite all this, the preparation of trisubstituted silyl enol ethers with high *E*,*Z* selectivity and broad substrate scope remains rare. Herein, based on our previous work of silyl glyoxylates,[6] we report a novel hydrogen-bond-assisted sequential reaction of silyl glyoxylates **1** and nitroethanols **2**, generating products with a high level of *E*,*Z* selectivity (up to 99:1 for *Z*-selectivity, and 9.2:1 for *E*-selectivity). To our knowledge, this reaction model via Henry reaction/Brook rearrangement/elimination or Henry reaction/Brook rearrangement/retro-Henry reaction/elimination processes[7] has not been reported.

Scheme 1. Synthesis of Trisubstituted Silyl Enol Ethers



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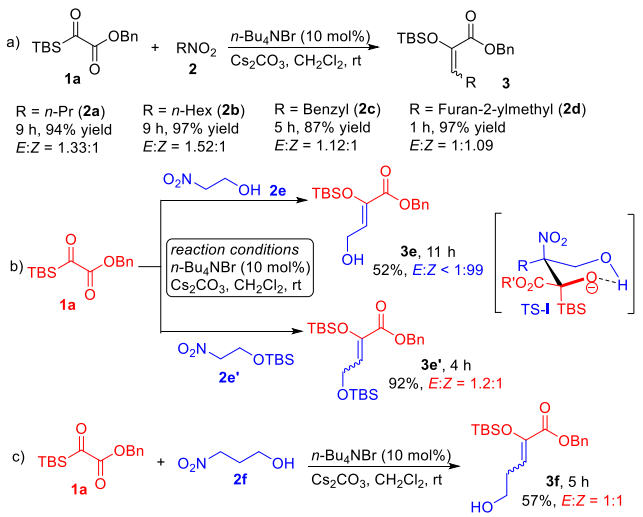
To realize this new sequential reaction, we first examined the reaction of 1-nitropropane **2a** with silyl glyoxylate **1a**[8] under PTC conditions.[9] Fortunately, the desired product **3a** was obtained in a yield of 94% (Scheme 2a). However, almost no

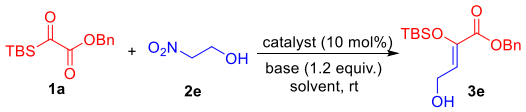
Scheme 2. Sequential Reaction of Silyl Glyoxylate 1a



selectivity (E/Z = 1.33:1 for **3a**) was observed. Subsequently, 1-nitrohexane (**2b**), (2-nitroethyl)benzene (**2c**), and 2-(2-nitroethyl)furan (**2d**) were examined as nucleophiles to investigate the reaction scope, and all of the reactions proceeded well, providing the products (**3b**−**3d**) in good yields (Scheme 2a). Based on chemical shifts of the olefinic protons, the stereochemistry of the products was determined by ^{1}H NMR spectra,[5a,10] and the data of product **3b** from Scheme 2a and **3ap** from Scheme 4a were consistent with the data from ref 5a. However, a mixture of geometric isomers (E/Z = 1.52:1−1:1.09) was achieved in all cases (Scheme 2a). Considering that the carbonyl group of silyl glyoxylate could be strongly activated by hydrogen bonds in our previous work,[6] we envisioned that nucleophiles with hydrogen groups, such as 2-nitroethanol (**2e**), may be beneficial to increase stereoselectivity. As shown in Scheme 2b, if hydrogen bonds between the alkoxide and OH group of **2e** formed after the nucleophilic addition of 2-nitroethanol (**2e**) to silyl glyoxylate (**1a**), the transition state (TS-**I**) was formed to enhance the selectivity obtained from the sequential reaction. To our delight, the Z-selectivity was greatly improved to 99:1 when the reaction was catalyzed by n-Bu$_4$NBr in dichloromethane. In contrast, a sharp decrease in stereoselectivity was observed by using a hydroxyl-protected substrate (**2e′**) under the same reaction conditions. However, geometric selectivity (E/Z = 1:1) decreased sharply with an increase in the alkyl chain length when 3-nitropropan-1-ol (**2f**) was employed as the nucleophile (Scheme 2c). These results indicated that hydrogen bonds are a crucial factor in controlling reaction selectivity.

To further improve the reaction efficiency, a model reaction of 2-nitroethanol (**2e**) to silyl glyoxylate (**1a**)[11] was chosen to optimize the conditions (Table 1). The control experiment results showed that no desired product was obtained in the absence of n-Bu$_4$NBr or Cs$_2$CO$_3$ (Table 1, entries 2 and 3). Inspired by these results, a series of catalysts was examined (Table 1, entries 4−7), and n-Bu$_4$NCl was found to improve the reaction in 4 h, generating the corresponding product in 72% yield with excellent Z-selectivity (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	base	time (h)	yield[b] (%)	E/Z[c]
1	n-Bu$_4$NBr	CH_2Cl_2	Cs_2CO_3	11	52	<1:99
2	–	CH_2Cl_2	Cs_2CO_3	11	–	–
3	n-Bu$_4$NBr	CH_2Cl_2	–	11	–	–
4	n-Pr$_4$NBr	CH_2Cl_2	Cs_2CO_3	8	25	<1:99
5	n-Bu$_4$NCl	CH_2Cl_2	Cs_2CO_3	4	72	<1:99
6	n-Bu$_4$NI	CH_2Cl_2	Cs_2CO_3	24	42	<1:99
7	n-Bu$_4$NBF$_4$	CH_2Cl_2	Cs_2CO_3	11	36	<1:99
8	n-Bu$_4$NCl	CH_2Cl_2	K_2CO_3	22	44	<1:99
9	n-Bu$_4$NCl	CH_2Cl_2	Na_2CO_3	28	41	<1:99
10	n-Bu$_4$NCl	CH_2Cl_2	$NaHCO_3$	42	20	<1:99
11	n-Bu$_4$NCl	CH_2Cl_2	KOH	5	40	<1:99
12	n-Bu$_4$NCl	DCE	Cs_2CO_3	24	29	<1:99
13	n-Bu4NCl	$CHCl_3$	Cs_2CO_3	24	25	<1:99
14	n-Bu$_4$NCl	toluene	Cs_2CO_3	3	35	<1:99
15	n-Bu$_4$NCl	EtOAc	Cs_2CO_3	2	48	1:16.2
16	n-Bu$_4$NCl	THF	Cs_2CO_3	0.2	25	<1:99
17	n-Bu$_4$NCl	DMF	Cs_2CO_3	0.2	12	<1:99
18	n-Bu$_4$NCl	EtOH	Cs_2CO_3	8	–	–
19	n-Bu$_4$NCl	CH_3OH	Cs_2CO_3	8	–	–
20	n-Bu$_4$NCl	CH_2Cl_2	Cs_2CO_3[d]	8	38	1:50
21	n-Bu$_4$NCl	CH_2Cl_2	Cs_2CO_3[e]	5	58	<1:99
22	n-Bu$_4$NCl[f]	CH_2Cl_2	Cs_2CO_3	24	26	<1:99

[a]Reactions were performed with **1e** (0.12 mmol), **2a** (0.10 mmol), base (1.2 mmol), and catalyst (10 mol %) in 1.0 mL of solvent and stirred for the indicated time at rt. [b]Isolated yield after purification by column chromatography. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]1.0 equiv of base was used. [e]2.0 equiv of base was used. [f]5 mol % of the catalyst was used. TBS = *tert*-butyldimethylsilyl. DCE = $ClCH_2CH_2Cl$.

Subsequently, screening of bases was carried out in CH_2Cl_2 and no further increased yield was observed (Table 1, entries 8−11). Next, other solvents, such as DCE, $CHCl_3$, toluene, EtOAc, THF, and DMF, were also tested, but none of them improved the reaction efficiency (Table 1, entries 12−17). Considering that a huge amount of hydrogen bonds in polar protic solvents and E/Z ratio of products may be disturbed, when the reaction was performed in polar protic solvent (EtOH or MeOH), no desired product was obtained (Table 1, entries 18 and 19). Notably, a further decrease in the amount of Cs_2CO_3 led to a decrease in Z-selectivity (Table 1, entry 20). By increasing the amount of Cs_2CO_3 to 2 equiv, the yield of product **3e** was decreased to 58% with excellent Z-selectivity (Table 1, entry 21). The decreased yield was observed when 5 mol % of a catalyst was applied in the reaction (Table 1, entry 22).

Under the optimal reaction conditions, a series of silyl glyoxylates were applied to the reaction (Table 2). Generally, silyl glyoxylates with halogen substituents were well tolerated, producing the corresponding trisubstituted silyl enol ethers (**3g**−**l**) with high stereoselectivity (E/Z ratio: 1:28 to <1:99). Both electron-withdrawing and electron-donating groups on the benzene ring of silyl glyoxylates proceeded well, generating the products (**3m**−**n**) with high stereoselectivity. Notably, the cyclohexyl-based ester group and ethyl group on the silyl

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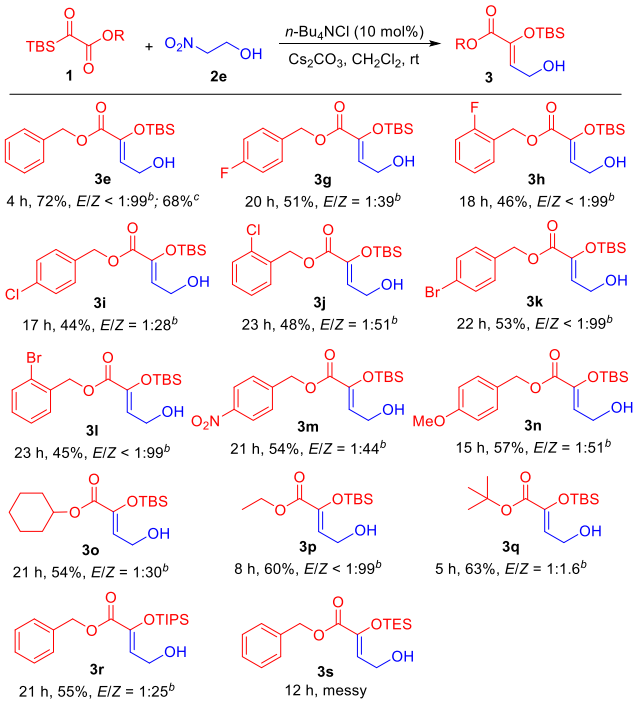
Table 2. Reaction Scope of Silyl Glyoxylates[a]



[a]Reactions were performed with **1** (0.10 mmol), **2e** (0.12 mmol), Cs_2CO_3 (1.2 mmol) and *n*-Bu_4NCl (10 mol %) in 1.0 mL of CH_2Cl_2. TIPS = triisopropylsilyl, TES = triethylsilyl. [b]Determined by ^1H NMR analysis of the crude mixture. [c]1.33 mmol scale.

glyoxylate were well tolerated, affording the corresponding products (**3o−p**) with high stereoselectivity. However, almost no stereoselectivity (*E*/*Z* = 1:1.6 for **3q**) was observed when a tertiary butyl ester group on the silyl glyoxylate was examined. Moreover, the reaction with a bulky TIPS group on the silyl glyoxylate proceeded well to furnish **3r** with high stereoselectivity. In contrast, messy products (**3s**) were observed when silyl glyoxylate bearing a TES group was applied to the reaction, possibly because the enol silyl ether bond in the product is sensitive to Cs_2CO_3.

Subsequently, 2-nitro-3-phenylpropan-1-ol (**2h**) was employed as the nucleophile in the reaction (Scheme 3). However, no tetrasubstituted silyl enol ether (**3c′**) was obtained, and the unexpected product of trisubstituted silyl enol ether (**3c**) was obtained with moderate *E*-selectivity. Interestingly, the retro-Henry reaction process was observed in this transformation (Scheme 3a). To further improve the stereoselectivity, different substituents on the silyl glyoxylate, such as 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, and 2-FC_6H_4, were examined, and the *E*-selectivity slightly increased to 4:1 when 2-ClC_6H_4 on the silyl glyoxylate was used as the substrate (Scheme 3b). Considering the steric hindrance effect, the bulky *tert*-butyl ester group may be beneficial for the selectivity. To our delight, the *E* isomer yield (**3t**) (*E*/*Z* = 7.3:1) was increased substantially when silyl glyoxylate (**1l**) with a *tert*-butyl ester group was employed (Scheme 3c).

With the optimal conditions for *E*-selectivity, we next turned our attention to the substrate scope of 2-nitroethanol derivatives.[12] Generally, different substituents on the benzene ring of 2-nitro-3-phenylpropan-1-ol were well tolerated. As shown in Table 3, halogen substituents, such as *p*-F, *o*-F, *m*-F, *p*-Cl, and *p*-Br on the benzene rings, were used as the substrate

Scheme 3. Sequential Reactions of 2h with Silyl Glyoxylates

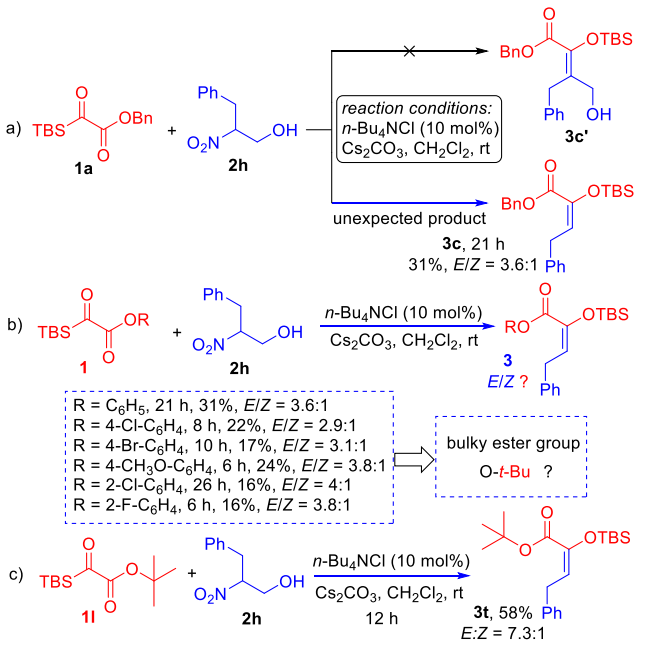
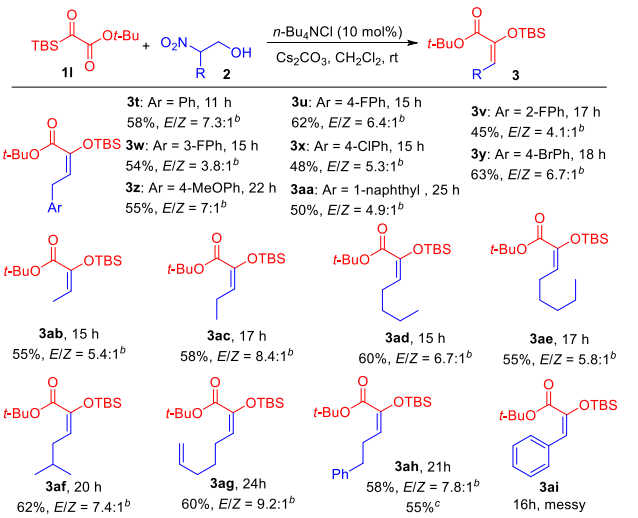


Table 3. Reaction Scope of 2-Nitroethanols



[a]Reactions were performed with **1l** (0.10 mmol), **2** (0.12 mmol), Cs_2CO_3 (1.2 mmol), and *n*-Bu_4NCl (10 mol %) in 1.0 mL of CH_2Cl_2. [b]Determined by ^1H NMR analysis of the crude mixture. [c]2.05 mmol scale.

and the reaction proceeded smoothly, generating the corresponding products (**3u−y**) with high *E*-selectivity. Moreover, high *E*-selectivity (**3z**) was obtained when the electron-donating group (OMe) on the benzene ring was employed as the substrate. However, a slight decrease in *E*-selectivity (**3aa**) was observed when the reaction of 1-(2-nitroethyl)naphthalene was carried out under the optimal conditions. Interestingly, the alkyl substituents on 2-nitroethanol were also suitable for the reaction, providing the product (**3ab**) with good *E*-selectivity. The reaction of silyl glyoxylate (**1l**) with an increase in the alkyl chain length in 2-nitroethanol derivatives does not affect the *E*-selectivity, yielding the products (**3ac−af**) with high selectivity. Vinyl and phenyl groups were also introduced to the 2-nitroethanol

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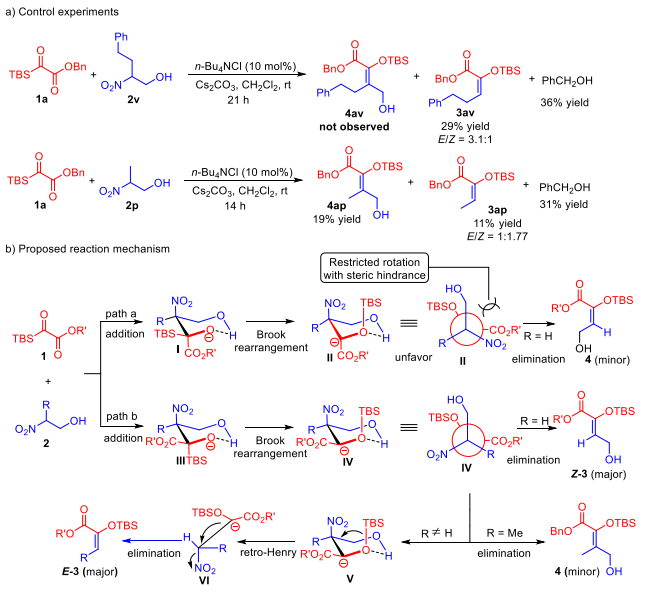
substrate, leading to products **3ag** and **3ah** with high *E*-selectivity. Further investigation showed that the reaction was sluggish with messy products (**3ai**) when 2-nitro-2-phenylethan-1-ol was used as the substrate. Furthermore, this sequential reaction was scaled up to 1.3 to 2.0 mmol for practical applications, generating **3e** and **3ah** in 68% and 55% yield, respectively.

To further investigate the reaction pathway, we reinvestigated the reaction of **1a** and **2v** under the optimal conditions (Scheme 4a). Because of the base reactions, a certain amount

Scheme 4. Control Experiments and Proposed Mechanism



of the hydrolysis product benzyl alcohol was obtained with a 36% yield in this transformation. However, no tetrasubstituted silyl enol ether (**4av**) was observed, and similar results for the preparationof **3c′** are also shown in Scheme 3a.

Considering that steric effects, such as the large size of the phenethyl substituent form **2v** and benzyl substituent form **2h**, have an unfavorable effect on elimination, the reaction of **1a** and 2- nitro ethanol **2p** with a small methyl group was conducted under the optimal conditions. Satisfyingly, the tetrasubstituted silyl enol ether product **4ap** was obtained via Henry reaction/Brook rearrangement/elimination processes. Moreover, a certain amount of the hydrolysis product benzyl alcohol was also obtained with a 31% yield. The experimental data and these control experiments indicated that the competitive relationship between the direct elimination process and retro-Henry reaction/elimination process and the product structure depend on the size of the substituent on the 2-nitroethanol derivatives. Moreover, compared to the hydrolysis processes of benzyl-based ester, the hydrolysis of tertiary butyl ester was inhibited due to its large steric hindrance and leaving group ability. Accordingly, the reaction mechanism proceeding via a competitive pathway was proposed. As shown in Scheme 4b, after the nucleophilic addition of nitroethanol (**2**) to silyl glyoxylate (**1**) under PTC conditions, intermediates **I** and **III** were obtained. To observe the elimination processes more easily, the chair forms **I** and **III** were proposed, and the nitro group (NO_2) was fixed at the axial bond. In these transformations, the alkoxide could be stabilized by hydrogen bonds from the OH group. Subsequently, intermediate **II** from path a was achieved after Brook rearrangement. Due to the restricted rotation with steric hindrance depicted in the Newman projection model **II**, *anti*-periplanar elimination is unfavored, generating minor product **4**. In contrast, the preferred conformation **IV** obtained from path b with the NO_2 group at the *anti*-periplanar position is favored for elimination, giving the *Z*-selectivity product *Z*-**3** when the R substituent is hydrogen. Interestingly, the retro-Henry process from **V** to **VI** occurred when the R substituent was not hydrogen, generating the *E*-selective product ***E*-3** as the major product.

In summary, we have developed a novel hydrogen-bond-assisted controlled sequential reaction of silyl glyoxylates. This method enables efficient geometric synthesis of trisubstituted silyl enol ethers with high selectivity. With the assistance of hydrogen bonds, the stereochemical outcome for both *E*- and *Z*-isomers depended on the structure of 2-nitroethanol and its derivatives. Further studies of new reactions of silyl glyoxylates are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03683.

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

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Notes

The authors declare no competing financial interest.

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