Rearrangements

Deutsche Ausgabe: DOI: 10.1002/ange.201604945
Internationale Ausgabe: DOI: 10.1002/anie.201604945

Highly Efficient Access to Both Geometric Isomers of Silyl Enol Ethers: Sequential 1,2-Brook/Wittig Reactions

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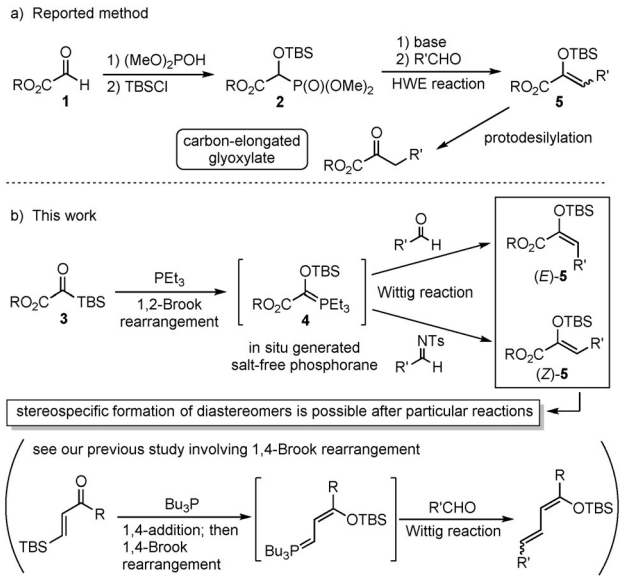
Abstract: *Novel sequential 1,2-Brook/Wittig reactions were developed for the preparation of silyl enol ethers. This method enables highly selective preparation of both geometric isomers of glyoxylate silyl enol ethers, using aldehydes (E-selective) and tosylimines (Z-selective) as a Wittig electrophile. The salt-free conditions of this reaction system are likely to be advantageous for switching the selectivity. The optimal reaction conditions and generality of the reaction were investigated, and plausible explanations for the observed selectivity were also discussed.*

Silyl enol ethers are recognized as versatile building blocks and have been utilized in numerous synthetic studies, for example, in Mukaiyama-type aldol reactions and Mannich-type reactions.[1] Among various types of silyl enol ethers, those having an electron-withdrawing group on the silyloxy-bearing carbon atom, such as **5** (Scheme 1), fall under an important category of synthetic intermediates and is mainly used as a synthon for a glyoxylate-type structure.[2] When transformation of a particular aldehyde into the glyoxylate-type structure is required, the reported method involves Horner–Wadsworth–Emmons (HWE) reaction of the carbanion of the phosphonate **2**, which can be prepared from the glyoxylate **1** in two steps, followed by protodesilylation of the resultant silyl enol ether **5** (Scheme 1 a).[2] In such cases, the geometry of **5** is not important because it has no relation to the stereochemistry of the glyoxylate products. In contrast, several valuable reactions involving **5** as a key substrate have increasingly been reported, such as [2+2] cycloaddition with ketenes,[3] vinylogous addition to vinylcarbenoids,[4] and heterocycle assembly by Mannich-type addition reactions.[5] In these cases, the alkene carbon atom bearing R′ can act as a prochiral carbon atom and provide a new stereogenic center after the reaction, and the issue of diastereoselectivity arises when other stereogenic centers exist in the product. Because the *E*,*Z* geometry of **5** is reflected in the relative position of R′ in the product, stereocontrolled preparation of **5** would be of great importance in such cases. Although base-induced deprotonation of an enolizable glyoxylate and subsequent silylation is the typical method for the preparation of **5**, it is difficult to realize a high level of *E*,*Z* selectivity with broad generality because thermodynamic and/or kinetic preferences for each enolate depend upon factors such as substituents and reaction conditions. In addition, even if one geometric isomer can be obtained with high selectivity, it will be difficult to prepare the other isomer from the same substrate under similar reaction conditions.



Scheme 1. Preparative methods of the glyoxylate silyl enol ethers **5**. TBS = *tert*-butyldimethylsilyl.

In the course of our ongoing research on the development of novel domino reactions based on silyl migration,[6] we recently reported the preparation of silyl dienol ethers by a 1,4-Brook rearrangement/Wittig reaction sequence (Scheme 1 b).[7] This finding inspired us to envisage that the silyl-substituted glyoxylate **3** could be transformed into the silyloxyphosphorane **4** by phosphine addition and 1,2-Brook rearrangement, which would be followed by a Wittig reaction to give **5** in a one-pot manner.[8] Gratifyingly, this strategy was realized for the highly selective formation of both geometric isomers by appropriate selection of the Wittig electrophiles, that is, either aldehydes (*E* selective), or tosylimines (*Z* selective). It was also demonstrated that the advantageous salt-free conditions of this protocol is indispensable for the effectiveness of the reaction. Herein, we disclose selective access to both geometric isomers of the synthetically useful **5** in one pot, starting from **3**.

We began the investigation of the sequential reaction using 4-chlorobenzaldehyde and benzyl *tert*-butyldimethylsilylglyoxylate (**3a**) as model substrates, and found that the reaction cleanly proceeded by employing a trialkylphosphine

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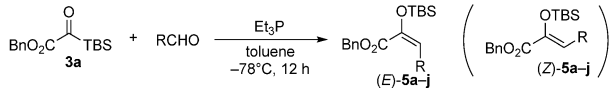
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604945.

(Me_3P, Et_3P, or nBu_3P) as a nucleophile in toluene to give the desired alkene **5b** in over 90% yield. Although the stereoselectivity was very poor at room temperature ($E/Z = 2:1$–$1:1$), the *E* selectivity was largely improved to 86:14 by conducting the reaction at −78 °C in the presence of Et_3P. The reaction is operationally simple, and the sequential 1,2-Brook rearrangement/Wittig reaction proceeds by mixing the three reagents in toluene at low temperature to afford the product with satisfactory *E* selectivity. Under the optimal reaction conditions, various aromatic and aliphatic aldehydes were examined (Table 1). In the case of aromatic aldehydes

Table 1: Reaction of **3** with aldehydes in the presence of PEt_3.[a]



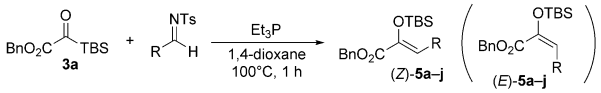
Entry	R	Product	Yield [%][b]	*E*/*Z*[c]
1	Ph	**5a**	quant.	81:19
2	4-ClC_6H_4	**5b**	90	86:14
3	4-MeC_6H_4	**5c**	96	84:16
4	1-naphthyl	**5d**	91	95:5
5	PhCH=CH (*E*)	**5e**	84	94:6
6	Me	**5f**	80	97:3
7	*n*Pr	**5g**	86	95:5
8	*i*Bu	**5h**	94	96:4
9	$PhCH_2CH_2$	**5i**	79	94:6
10[d]	cyclohexyl	**5j**	77	>99:1

[a] Triethylphosphine (0.075 mmol) was added to a solution of glyoxylate (0.1 mmol) and aldehyde (0.05 mmol) in toluene at −78 °C. [b] Yield of products as a mixture of *E*/*Z* isomers. [c] The ratio was estimated by ^{1}H NMR analysis. [d] The reaction was carried out at −20 °C.

(entries 1–4), high chemical yields were attained in every case (>90%) with predominant *E* selectivity. The sterically demanding 1-naphthylaldehyde resulted in a high level of *E* selectivity (entry 4). Cinnamaldehyde was also shown to be highly stereoselective, thus affording the corresponding *E*,*E*-diene product **5e** (entry 5), which is expected to be a good substrate for Diels–Alder cycloadditions. Various aliphatic aldehydes afforded satisfactory results with regard to both *E* selectivity and chemical yield (entries 6–10). These results demonstrated applicability of the reaction for a wide range of aldehydes. In all cases, the two geometric isomers could be separated by silica gel column chromatography.[9] Therefore, *E* isomers could be conveniently isolated in pure form in practical yields.

While aldehydes have been more frequently utilized as the reactive electrophilic partner in Wittig reactions, several attempts to employ imine compounds as a surrogate for aldehydes in Wittig reactions have also been reported.[10] For example, N-arylimines reacted with phosphoranes to yield alkenes and iminophosphorane, via an aza-phosphetane intermediate, through the Wittig-type reaction pathway.[11] More recently, Tian and co-workers revealed that electron-deficient imines such as N-sulfonylimines worked well in such reactions under milder reaction conditions and with tunable stereoselectivity depending on the sulfonyl substituents.[12] In this context, we conducted a trial with N-tosylimines instead of aldehydes as the Wittig electrophile. First, we applied the same reaction conditions as used for the aldehydes (Table 1), to the reaction of **3a** with *N*-tosylbenzaldimine. These attempts, however, were fruitless, and the reaction did not proceed at either −78 °C or room temperature, probably because of the steric bulk of the tosyl group, relative to that of the aldehydes, as well as the poor solubility of the N-tosylimine in toluene. Moreover, rapid formation of a relatively stable adduct complex between the N-tosylimine and Et_3P would interrupt the desired reaction.[13] Taking these factors into consideration, the reaction was performed at 100 °C in 1,4-dioxane, and the N-tosylimine was added slowly, after the addition of phosphine to a solution of **3a**. To our delight, this change in protocol led to a successful 1,2-Brook/Wittig reaction sequence, and the results using various N-tosylimines under the optimal reaction conditions are summarized in Table 2. Aromatic imines gave excellent chemical

Table 2: Reaction of **3** with N-tosylimines in the presence of PEt_3.[a]



Entry	R	Product	Yield [%][b]	*E*/*Z*[c]
1	Ph	**5a**	92	<1:99
2	4-ClC_6H_4	**5b**	93	6:94
3	4-MeC_6H_4	**5c**	99	7:93
4	1-naphthyl	**5d**	98	2:98
5	PhCH=CH (*E*)	**5e**	84	12:88
6	Me	**5f**	–[d]	–
7[e]	*n*Pr	**5g**	51	8:92
8	*i*Bu	**5h**	87	30:70
9	$PhCH_2CH_2$	**5i**	49	36:64
10	cyclohexyl	**5j**	34	34:66

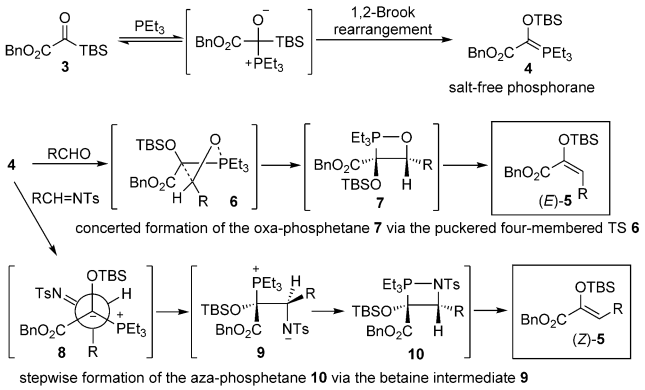
[a] Triethylphosphine (0.075 mmol) was added dropwise to a solution of glyoxylate (0.1 mmol) in 1,4-dioxane, and then a solution of N-tosylimine (0.05 mmol) in 1,4-dioxane was added to the mixture at 100 °C. [b] Yield of isolated product as a mixture of *E*/*Z* isomers. [c] The ratio was estimated by ^{1}H NMR analysis. [d] The substrate imine was rather unstable under the reaction conditions and reproducibility of the results was not possible. [e] The reaction time was 3 h. Ts = 4-toluenesulfonyl.

yields (over 90%) and stereoselectivities (entries 1–4), and importantly, the *Z* isomers [(*Z*)-**5a**–**d**] were obtained as the major product. These results present a striking contrast to those ooptained with aldehydes, which predominantly provided the *E* isomers [(*E*)-**5a**–**d**]. The same *Z* selectivities were observed when using an α,β-unsaturated imine (entry 5) and aliphatic imines (entries 7–10). However, for of aliphatic imines the chemical yields were slightly lower because of the instability of the imines compared with those of the aromatic ones, and the *Z* selectivities were moderate.

Thus, the two protocols of sequential 1,2-Brook/Wittig reactions presented, using either aldehydes (Table 1) or N-tosylimines (Table 2), provide a methodology for preparing both (*E*)-**5** and (*Z*)-**5** with high efficiency. The work of Tian and co-workers on the reaction of phosphoranes and N-sulfonylimines to give either *E* or *Z* alkenes demonstrates a remarkable change in *E*,*Z* selectivity by tuning of the

sulfonyl substituents, namely, aromatic sulfonyl groups (*Z*-selective) versus aliphatic sulfonyl groups (*E*-selective).[12] In contrast, changing the N-sulfonyl substituents (from Ts to $MeSO_2$, $BnSO_2$, etc.) did not affect the degree of the *Z* selectivity in our case. Consequently, the dramatic change in *E*,*Z* selectivity observed in this study is attributed to differences in the chemical properties between aldehydes and N-sulfonylimines.

A possible explanation for the observed selectivity is proposed in Scheme 2. Addition of triethylphosphine to the

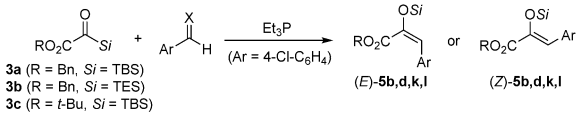


Scheme 2. Plausible reaction mechanism for the formation of (*E*)-**5** and (*Z*)-**5**.

silylglyoxylate and subsequent 1,2-Brook rearrangement generates the salt-free phosphorane **4**. Wittig reactions of **4** with aldehydes proceed via a puckered four-membered transition-state (**6**), in which R is directed to the space far from the bulky silyloxy group to give the oxa-phosphetane **7**, which provides (*E*)-**5** after elimination of phosphine oxide. In general, oxa-phosphetane formation in the Wittig reaction is known to be a concerted [2+2] cycloaddition process without a betaine intermediate,[14] and salt-free conditions preclude the reversibility between **7** and **4** (and aldehyde).[15] Therefore, the reaction would be kinetically controlled even if **4** is stabilized by the ester carbonyl group, and the transition state with the lowest energy, such as **6**, would dictate the stereochemical outcome. In contrast, the reaction of phosphoranes with N-sulfonylimines to form aza-phosphetanes has been reported to involve betaine intermediates, and the two reactants would approach with an *anti*-periplanar arrangement of the sulfonylimino group and the phosphonium group.[12b,c] Thus, in the present cases, the aza-phosphetane **10** would be formed via the betaine intermediate **9**, formed by an approach depicted in the Newman projection model **8**, in which R is oriented *anti* to the sterically demanding silyloxy group and thus leads to the dominant production of (*Z*)-**5**.

Consideration of the stereoselectivity discussed in Scheme 2 suggests that sterics around the silyl group and the ester moiety of **4** would significantly influence the selectivity. Indeed, it was found that the combination of the TBS group and benzyl ester was crucial for the selective preparation of both geometric isomers. Selected examples are shown in Table 3 (entries 1–6). Compared to the reference

Table 3: Reaction of various silyl glyoxylates **3** with either an imine or aldehyde in the presence of PEt_3.[a]



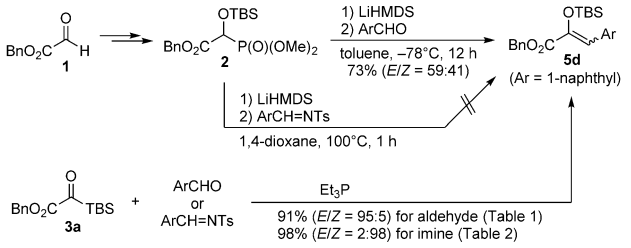
Entry	X	R	*Si*	Yield [%][b]	*E*/*Z*[c]
1	O	Bn	TBS	90 (**5b**)	86:14
2	O	Bn	TES	86 (**5k**)	49:51
3	O	*t*Bu	TBS	82 (**5l**)	51:49
4	NTs	Bn	TBS	93 (**5b**)	6:94
5	NTs	Bn	TES	94 (**5k**)	11:89
6	NTs	*t*Bu	TBS	48 (**5l**)	11:89
7[d]	O	Bn	TBS	quant. (**5b**)	65:35
8[d,e]	NTs	Bn	TBS	50 (**5d**)	18:82

[a] When using aldehyde, the reaction was performed in toluene at −78 °C. In the cases an imine the reaction was performed in 1,4-dioxane at 100 °C. [b] Yield of isolated product as a mixture of *E*/*Z* isomers. [c] The ratio was estimated by ^{1}H NMR analysis. [d] In the presence of 1 equivalent of $LiClO_4$. [e] 1-Naphthyl-*N*-tosylimine was used (Ar = 1-naphthyl). TES = triethylsilyl.

experiment using an aldehyde (entry 1), a decrease in the silyl bulk (from TBS to TES) or an increase in the ester bulk (from Bn to *t*Bu) resulted in considerable loss of the stereoselectivity (entries 2 and 3). The same experiments were performed for the N-sulfonylimine, and it was found that the selectivity was also affected (entry 4 versus entries 5 and 6) and the yield was largely lowered when using sterically congested substituents (entry 6). Thus, **3a**, possessing the TBS group and the benzyl ester, was found to be the best substrate for efficient and selective synthesis of (*E*)-**5** and (*Z*)-**5**. Another noteworthy point of the present reaction is that salt-free phosphoranes can be prepared by the 1,2-Brook rearrangement, unlike the typical phosphorane preparation which requires base treatment of a phosphonium salt. In fact, the stereoselectivities were severely affected in the presence of a lithium salt (entry 7 versus entry 1, entry 8 versus entry 4 of Table 2), thus suggesting an advantage of the sequential 1,2-Brook/Wittig reaction system for practical selectivity.

As already introduced in Scheme 1, **5** bearing an ester moiety has been widely utilized as a versatile synthetic building block, and is usually prepared through the HWE reaction of **2**. Accordingly, we carried out this reported method and compared it with the present reaction system (Scheme 3). The phosphonate **2**, prepared from **1**, was treated with LiHMDS and then reacted with 1-naphthylaldehyde in toluene at −78 °C to afford **5d** in 73 % yield with considerably low stereoselectivity (*E*/*Z* = 59:41). When using the corresponding N-tosylimine as a Wittig electrophile, the reaction gave a complex mixture and the desired product **5d** could not be detected. These results demonstrated that the sequential 1,2-Brook/Wittig reaction using **3a** is clearly advantageous in both yield and selectivity, as shown in Table 1 and Table 2 (entry 4).

In summary, we have described a novel 1,2-Brook/Wittig reaction sequence which provides synthetically useful glyoxylate silyl enol ethers in a stereoselective manner. A simple change of the Wittig electrophile led to a switch in the



Scheme 3. Comparison of the reported method with the present study. HMDS = hexamethyldisilazide.

stereochemical outcome (aldehydes and tosylimines provided *E* and *Z* isomers, respectively). Salt-free conditions are likely to be a critical factor for this selectivity, because such conditions would minimize the reversibility of the reaction process and prevent thermodynamic control of the *E*,*Z* isomers. Extension of these studies to various silyl enol ether preparations are currently ongoing in our laboratory.

Experimental Section

General procedure for the reaction of compound **3** with aldehydes: To a solution of benzyl *tert*-butyldimethylsilylglyoxylate (**3a**) (0.20 mmol) in dry toluene (0.5 mL) was added aldehyde (0.10 mmol), and then the solution was cooled to −78 °C. Triethylphosphine (20 % in toluene, 0.20 mmol) was added dropwise via syringe, and the solution was stirred at the same temperature for 12 h. After the reaction was quenched with water, the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give (*E*)-**5** with small amount of (*Z*)-**5** as a colorless oil.

General procedure for the reaction of compound **3** with sulfonylimines: To a solution of benzyl *tert*-butyldimethylsilylglyoxylate (**3a**) (0.20 mmol) in dry 1,4-dioxane (0.5 mL) was added triethylphosphine (20 % in toluene, 0.15 mmol) at 100 °C. A solution of sulfonylimine (0.10 mmol) in 1,4-dioxane (0.5 mL) was added dropwise via syringe, and the solution was stirred at the same temperature for 1 h. The same work-up procedure mentioned above gave (*Z*)-**5** with small amount of (*E*)-**5** as a colorless oil.

Acknowledgments

This work was supported in part by the KAKENHI, a Grant-in-Aid for Encouragement of Young Scientists (B: 26860011).

Keywords: phosphines · reaction mechanisms · rearrangements · silicon · stereoselectivity

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10079–10082
Angew. Chem. **2016**, *128*, 10233–10236

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Received: May 20, 2016
Published online: July 12, 2016

