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Synthesis of β-branched Morita–Baylis–Hillman-type adducts from 1,3-diaryl-2-propynyl trimethylsilyl ethers and aldehydes catalyzed by potassium *tert*-butoxide

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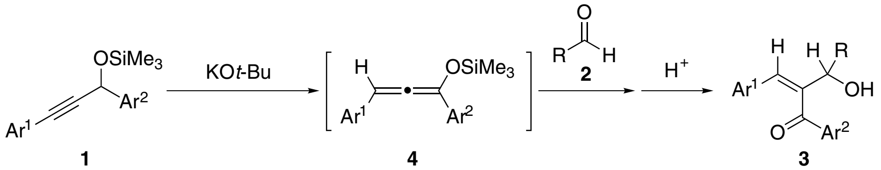
Abstract—1,3-Diaryl-2-propynyl trimethylsilyl ethers were easy to isomerize into the corresponding siloxyallenes using a catalytic amount of potassium *tert*-butoxide under very mild conditions. The siloxyallenes reacted in situ with various aldehydes to afford *Z*-selective β-branched Morita–Baylis–Hillman-type adducts in a one-pot reaction after acid treatment.

Morita–Baylis–Hillman-type adducts have attracted wide interest among numerous researchers as useful intermediates. To the best of our knowledge, β-branched Morita–Baylis–Hillman-type adducts are not always obtained by the general Morita–Baylis–Hillman reaction, so improved methods to acquire these compounds have been developed to overcome this limitation. Most of the improved methods involve 1-acylethenyl or allenoxy metal intermediates derived from α,β-acetylenic carbonyl or α-halo-α,β-unsaturated carbonyl compounds, followed by coupling with the appropriate aldehydes or ketones.[1] It has also been reported that β-branched Morita–Baylis–Hillman-type adducts can be obtained via the intermediates from 2-alkynyl alcohols or their derivatives.[2] As a method not using metals, there are methods using the α-carbanion generated from α-silyl-α,β-unsaturated carbonyl derivatives.[3] Moreover, a few approaches to the adduct using siloxyallenes derived from silyl ketones have been reported.[4]

We recently reported that quaternary ammonium fluorides derived from cinchonine catalyzed the reaction of 1-phenyl-2-(trimethylsilyl)acetylene with aromatic aldehydes to produce the *Z*-selective β-branched Morita–Baylis–Hillman-type adducts substituted by poly-aryl groups.[5] It was also reported that a base besides the fluoride ion might play a key role in this reaction. During the course of the study about the mechanism, it was found that 1,3-diaryl-2-propynyl trimethylsilyl ethers **1** were easy to isomerize into the corresponding siloxyallenes **4** using a catalytic amount of potassium *tert*-butoxide (KO*t*-Bu) under very mild conditions, and siloxyallenes **4** reacted in situ with various aldehydes **2** to afford *Z*-selective β-branched Morita–Baylis–Hillman-type adducts **3** in a one-pot reaction after acid treatment, as shown in Scheme 1. We now wish to report this novel synthesis of β-branched Morita–Baylis–Hillman-type adducts from the silyl derivatives of 2-alkynyl alcohols.



Scheme 1.

Keywords: Morita–Baylis–Hillman adduct; Siloxyallene; Stereoselectivity; Isomerization.

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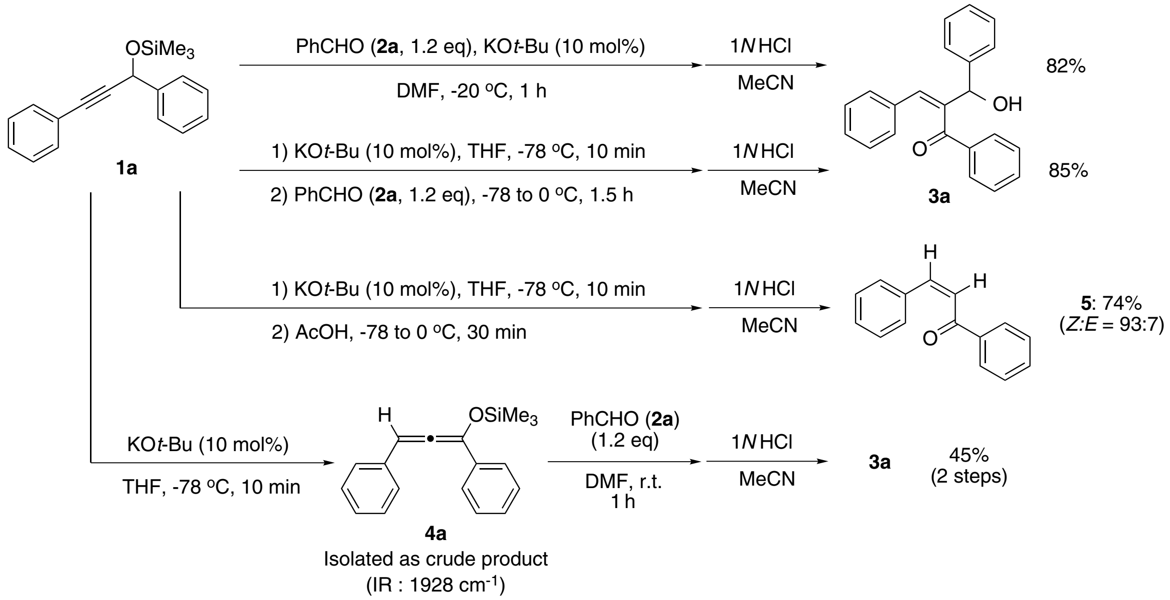


Scheme 2.

First of all, the reaction was investigated using the representative 1,3-diaryl-2-propynyl trimethylsilyl ether **1a** and benzaldehyde (**2a**), as shown in Scheme 2. Although a mixture of silyl ether **1a** and benzaldehyde (**2a**) in DMF efficiently and selectively afforded the *Z*-adduct **3a** using a catalytic amount of KO*t*-Bu at −20 °C after acid treatment (method A), **3a** was also obtained by the treatment of silyl ether **1a** with KO*t*-Bu in THF at −78 °C followed by the addition of **2a** after acid treatment (method B). The treatment of the mixture in DMF did not react at −78 °C similar to a stepwise process. When acetic acid was used instead of benzaldehyde (**2a**), the uncommon *Z*-chalcone **5** was stereoselectively obtained.[4a,6] This procedure is expected to become an option as a method for the synthesis of the *Z*-chalcone derivatives. After the treatment of the silyl ether **1a** with KO*t*-Bu in THF, **1a** isomerized into siloxyallene **4a** within 10 min, and allene **4a** could be isolated as a crude product, which could not be purified by silica gel column chromatography. The isomerization progressed under very mild conditions compared with the general isomerization from alkynes to allenes.[7] In DMF, **4a** could not be isolated as in THF due to its decomposition. The structure of **4a** was confirmed by specific infrared absorption of the allene moiety at about 1928 cm^{-1}.[8] Furthermore, it was observed that the crude siloxyallene **4a** reacted with **2a** to afford **3a** in DMF not using any catalysts. In THF, the crude **4a** did not react with **2a**.

Various aldehydes **2** undergo the reaction of 1,3-diphenyl-2-propynyl trimethylsilyl ether **1a** to give the Morita–Baylis–Hillman-type adducts **3** having the *Z*-configuration in moderate to good yields, as shown in Table 1. In all cases, when the reaction did not easily proceed by method A, method B was effective, and all aldehydes gave products **3**. The difference between the electron-donating and withdrawing groups on the aromatic ring did not influence the reaction (entries 1–4). Though the reaction of **1a** and aldehydes substituted by some other functional groups progressed by method A, the products were obtained in higher yield when using method B (entries 5–9). Especially, 4-nitrobenzaldehyde (**2f**), which did not react at all by method A, underwent the reaction to give **3f** using method B. The sterically hindered aldehyde **2g** also gave adduct **3g** without any extreme decrease in the yield (entry 10). The reaction with heterocyclic aldehydes **2h–j** also proceeded to give adducts **3h–j** (entries 11–14). However, the yield of **3j** was relatively low. When *trans*-cinnamaldehyde reacted with **1a**, adduct **3k** was obtained in moderate yield and the corresponding 1,4-adduct was not observed (entries 15 and 16). In the case of the aliphatic aldehydes, the reaction smoothly proceeded if the activated proton was not at the α-position (entry 17). In the reaction with isobutyraldehyde and valeraldehyde, many structural unknown compounds were observed by method A, and no adducts were obtained. However, method B effectively produced **3m** and **3n**, respectively (entries 18–21).

Next, the combination of substituents of trimethylsilyl ether **1**[9] and aldehydes or ketones **2** was continuously investigated, as shown in Table 2. As for the substituents of the products, various combinations were possible, and the difference between the electron-donating and withdrawing groups did not influence the reaction similar to the results in Table 1 (entries 1–5). Though **3t** and **3u** substituted by heterocyclic groups were obtained by method A in good yields, method B was effective for the synthesis of **3v** (entries 6–9). When silyl ether **1** had the cinnamyl moiety at the propargylic position instead of the aryl group, **1w** was deactivated and the yield of adduct **3w** was lower (entries 10 and 11). The product was formed in low yield or not obtained at all when either of the substituents of silyl ethers, **1x** and **1y**, is an alkyl group. Isomerization of the silyl ether **1**

Table 1. Reaction of silyl ether **1a** (Ar^1, Ar^2 = Ph) with aldehydes **2**

Entry	Product	R	Method[a]	Yield (%)[b]
1	**3a**	C_6H_5	A	82
2	**3a**	C_6H_5	B	85
3	**3b**	4-ClC_6H_4	A	76
4	**3c**	4-$MeOC_6H_4$	A	72
5	**3d**	4-$Me_2NC_6H_4$	A	35
6	**3d**	4-$Me_2NC_6H_4$	B	74
7	**3e**	4-$MeO_2CC_6H_4$	B	83
8	**3f**	4-$NO_2C_6H_4$	A	—
9	**3f**	4-$NO_2C_6H_4$	B	67
10	**3g**	2,6-$Me_2C_6H_3$	A	68
11	**3h**	2-Furyl	A	95
12	**3i**	2-Thienyl	A	83
13	**3j**	2-Pyridyl	A	35
14	**3j**	2-Pyridyl	B	54
15	**3k**	*trans*-$C_6H_5CH{=}CH$	A	52
16	**3k**	*trans*-$C_6H_5CH{=}CH$	B	66
17	**3l**	$(CH_3)_3C$	A	67
18[c]	**3m**	$(CH_3)_2CH$	A	—
19[c]	**3m**	$(CH_3)_2CH$	B	69
20[c]	**3n**	$CH_3CH_2CH_2CH_2$	A	—
21[c]	**3n**	$CH_3CH_2CH_2CH_2$	B	67

[a] For method A or B, see Ref. 11.
[b] Isolated yield.
[c] Aldehyde (1.5 equiv) was used.

into the corresponding siloxyallene by method B was not observed (entries 12 and 13). In the case of the reaction with ketones, general ketones, for example, 3-pentanone and acetophenone, did not produce any products. However, trifluoroacetophenone gave product **3z** in good yield (entry 14).

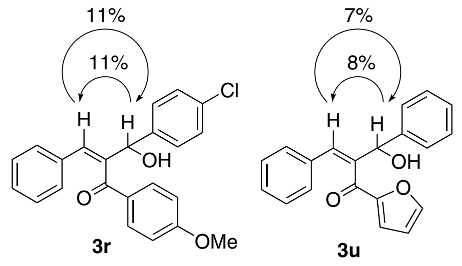


Figure 1.

In all cases, only the *Z*-isomers **3** were obtained and the signals assumed to be the *E*-isomer were difficult to observe in the ^{1}H NMR spectra of the crude product. The stereochemistries of the products were confirmed by a ^{1}H NMR (NOE) experiment of the representative products, **3r** and **3u**, shown in Figure 1. The relative configuration of the olefin of the other products **3** was assigned by analogy.

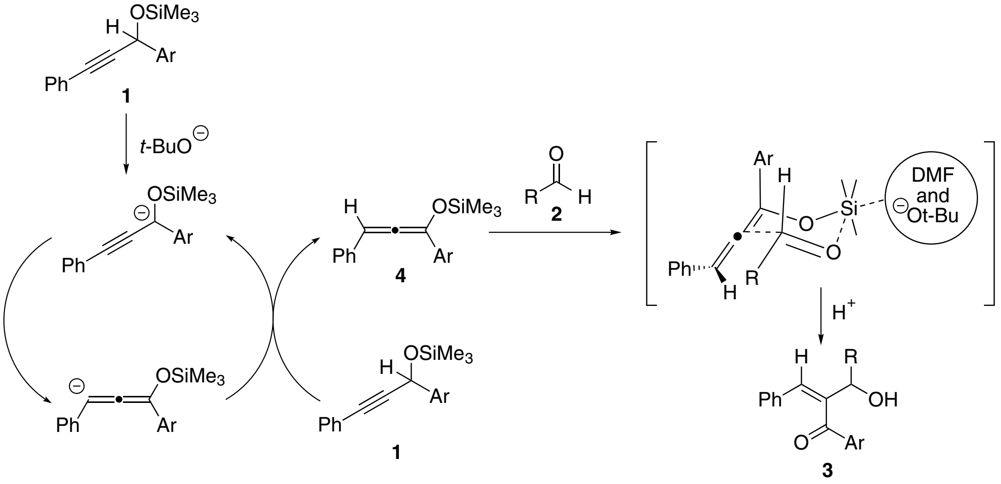
The proposed mechanism is depicted in Scheme 3 for the reaction. KO*t*-Bu serves as an initiator of the reaction, not as a catalyst in the cycle, because there was no change in the deuterium ratio of the product obtained from the silyl ether substituted by deuterium in the presence of *t*-BuOH (Scheme 4). Next, the allenic anion was protonated by the remaining **1** to give siloxyallene **4**. Finally, the aldol reaction of **4** with **2** was promoted by a Lewis base[10] to afford the *Z*-isomer **3**. Though this reaction was attempted using a catalytic amount of *n*-BuLi instead of KO*t*-Bu to confirm whether the reaction progresses even if other general bases are used, the isomerization hardly progressed. The reaction did not progress even when the amine, for example, *N*,*N*-diisopropylethylamine, was used.

In summary, we have found the high reactivity of 1,3-diaryl-2-propynyl trimethylsilyl ethers **1**, which were easy to isomerize into the corresponding siloxyallenes **4** by a catalytic amount of KO*t*-Bu under very mild conditions. Siloxyallenes **4** reacted in situ with various aldehydes **2** and trifluoroacetophenone to selectively afford the *Z*-β-branched Morita–Baylis–Hillman-type adducts **3** in a one-pot reaction after acid treatment. A further extension of this reaction is now actively in progress.

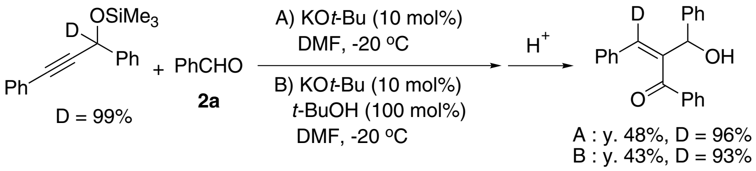
Table 2. Reaction of silyl ethers **1** with aldehydes **2**

Entry	Product	Ar^1	Ar^2	R	Method[a]	Yield (%)[b]
1	**3o**	C_6H_5	4-ClC_6H_4	C_6H_5	A	74
2	**3p**	C_6H_5	4-ClC_6H_4	4-$MeOC_6H_4$	A	71
3	**3q**	C_6H_5	4-$MeOC_6H_4$	C_6H_5	A	83
4	**3r**	C_6H_5	4-$MeOC_6H_4$	4-ClC_6H_4	A	83
5	**3s**	C_6H_5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	A	79
6	**3t**	C_6H_5	2-Furyl	C_6H_5	A	80
7	**3u**	C_6H_5	2-Thienyl	C_6H_5	A	76
8	**3v**	C_6H_5	2-Pyridyl	C_6H_5	A	40
9	**3v**	C_6H_5	2-Pyridyl	C_6H_5	B	78
10	**3w**	C_6H_5	*trans*-$C_6H_5CH{=}CH$	C_6H_5	A	28
11	**3w**	C_6H_5	*trans*-$C_6H_5CH{=}CH$	C_6H_5	B	50
12[c]	**3x**	*n*-C_4H_9	C_6H_5	C_6H_5	A	23
13	**3y**	C_6H_5	*n*-C_4H_9	C_6H_5	A	—
14[d]	**3z**	C_6H_5	C_6H_5	$C_6H_5COCF_3$	B	78[e]

[a] For method A or B, see Ref. 11.
[b] Isolated yield.
[c] KO*t*-Bu (20 mol %) was used.
[d] $C_6H_5COCF_3$ (1.5 equiv) was used instead of aldehyde.
[e] Product was obtained as trimethylsilyl ether of **3z**.



Scheme 3.



Scheme 4.

Acknowledgments

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8. The calculated value of infrared absorption using RHF/6-31G(d) was 1968 cm^{-1}.
9. Trimethylsilyl ether **1** was synthesized as follows. The alkyne lithiated with *n*-BuLi reacted with aldehydes to afford 2-alkynyl alcohols, followed by trimethylsilylation using triethylamine and chloro trimethylsilane.
10. For the aldol reaction of trimethylsilyl enolate with an aldehyde catalyzed by *tert*-butoxide as a Lewis base, see: Fujisawa, H.; Nakagawa, T.; Mukaiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1241–1246.
11. A typical procedure for the preparation of the Morita–Baylis–Hillman-type product **3** is as follows. Method A: To a solution of **1** (1.0 mmol) and **2** (1.2 mmol) in DMF (2 mL) was added KO*t*-Bu (0.1 mmol) at −20 °C under Ar. After 1 h, 1 N aq HCl (1 mL) and acetonitrile (2 mL) were added, and the mixture was stirred at room temperature for a few minutes. Water and EtOAc were added, and the separated organic layer was washed with water and brine, and dried over $MgSO_4$. After removal of the

solvent in vacuo, the residue was purified by silica gel column chromatography to give adduct **3**. Method B: To a solution of **1** (1.0 mmol) in THF (2 mL) was added 1 M KO*t*-Bu in THF (0.1 mmol) at −78 °C under Ar. After 10 min, **2** (1.2 mmol) was added, then the mixture was warmed to 0 °C in 30 min. After 1 h, 1 N aq HCl (1 mL) and acetonitrile (2 mL) were added, followed by a work-up procedure similar to that of method A.