α-Substituted acylsilanes *via* a highly selective [1,4]-Wittig rearrangement of α-benzyloxyallylsilane†

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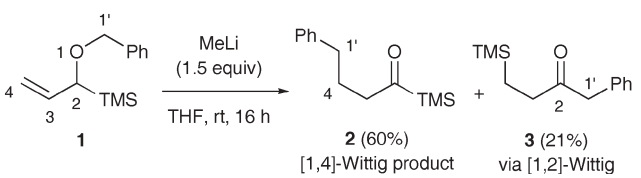
α-Benzyloxyallylsilane undergoes efficient [1,4]-Wittig rearrangement to generate an enolate intermediate that can be trapped with various electrophiles, thereby providing a new synthetic approach to substituted acylsilanes.

Wittig rearrangements of α-lithiated ethers have proven to be a valuable tool for organic chemists.[1] Among these rearrangements the [2,3]-Wittig is certainly the most studied and synthetically mature.[1,2] Similarly, the [1,2]-Wittig rearrangement has also been the subject of numerous mechanistic and synthetic studies,[1] many of which have come out of the labs of Nakai and Tomooka. Their investigations,[3] and those of several other groups,[4] have shed considerable light on the unique stereochemical aspects of this radical–radical anion dissociation–recombination. Allylic ethers are also capable of a [1,4]-Wittig rearrangement.[5] Nonetheless, relative to its [1,2]- and [2,3]-counterparts, the [1,4]-Wittig remains a reaction with many unanswered questions. For example, whether the [1,4]-mechanism is concerted or involves a radical–radical anion dissociation–recombination is still debated.[5c,d,f] The substrate scope of the [1,4]-Wittig is also not well documented and thus its potential in synthetic organic chemistry is unclear. Moreover, for substrates capable of both pathways, a strong preference for [1,4] over [1,2] bond reorganization is rarely realized,[5f,g,h,i] with Tomooka's very recent report of a highly selective [1,4]-silyl migration being a relevant exception.[5j]

During the course of an earlier study on the MeLi-promoted Wittig rearrangements of α-alkoxysilanes,[6] we found that, upon deprotonation, α-benzyloxyallylsilane **1** rearranged to afford a mixture of the [1,4]-Wittig product (**2**) and a second compound (**3**) derived from the [1,2]-Wittig product,[7] with acylsilane **2** favored by a ratio of 3:1 (Scheme 1). Owing to the aforementioned questions concerning the [1,4]-Wittig combined with recent developments by Scheidt,[8] Johnson,[9] and others[10] on the use of acylsilanes in organic synthesis, we decided to learn more about this reaction. Specifically, we were interested in increasing the [1,4]/[1,2] ratio and taking advantage of the enolate formed during the [1,4]-sigmatropic shift. Furthermore, we envisaged that information gathered during such a study would be helpful in future investigations directed at mechanistic inquiries.



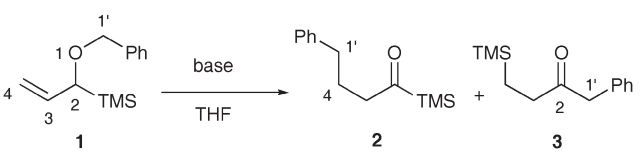
Scheme 1 Wittig rearrangement of α-alkoxysilane **1**.

As a general rule,[1,5f,11] Wittig rearrangements are sensitive to the base used to generate the α-lithiated ether and the temperature at which the reaction is run. Thus these seemed reasonable variables to examine initially during the rearrangement of **1** (Table 1).

Employing 1.5 equivalents of a 1.4 M solution of MeLi in diethyl ether as base, compound **1** was rearranged under a variety of temperatures. These experiments revealed that temperature clearly affects the ratio of [1,4]- *vs.* [1,2]-products. Per our goal, the [1,2]-Wittig pathway could be effectively suppressed when the reaction temperature was kept below −60 °C. However, at this temperature, the reaction was very slow and was incomplete after 72 h. Employing a greater excess of MeLi (3–4 equiv.) and higher temperatures (−37 °C) led to complete consumption of the starting material; however reaction times remained long (65–72 h) and under these conditions the [1,4]:[1,2] selectivity eroded (4:1). With MeLi as base, the combined yield of the [1,4]- and [1,2]-products typically averaged ~68%

With these preliminary temperature studies complete, we tested different alkylithium bases in the reaction. The results are summarized in Table 1. *n*-BuLi proved to be superior to MeLi, leading to complete conversion of the substrate (1.5 equiv. of base, −78 °C, 5 h) and affording the [1,4]-product selectively ([1,2]

Table 1 Optimizing the [1,4]-Wittig rearrangement of **1**



Entry	Base	Base equivalents	Temperature/ °C	Time/h	Yield (%)	[1,4]:[1,2]
1	MeLi	1.5–2.0	18 to 20	1.0	69	1.4:1 to 2:1
2	*n*-BuLi	1.5	18 to 20	1.0	68	2.45:1
3	MeLi	3.0	−80 to −37	72	68	4:1
4	*n*-BuLi	1.5	−80 to −37	2	83	9.1:1
5	*s*-BuLi	1.5	−50 to −37	<0.1	79–83	>20:1
6	MeLi	3.0	−80 to −50	72	68	>12:1
7	*n*-BuLi	1.5	−80 to −75	<5	79–83	>100:1[a]
8	*s*-BuLi	1.5	−80 to −75	<0.5	79–83	>100:1[a]

[a] [1,2]-Wittig product **3** was not detected (by TLC, ^{1}H NMR or GC-MS).

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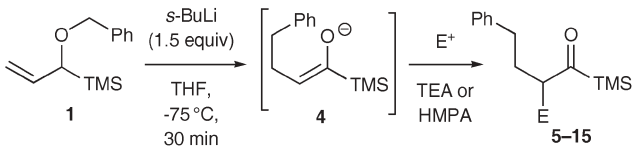
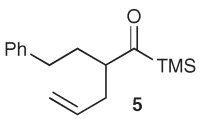
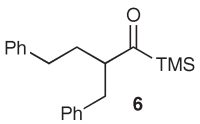
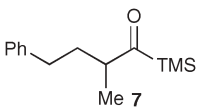
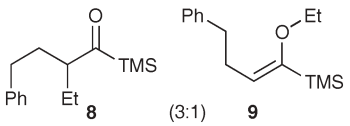
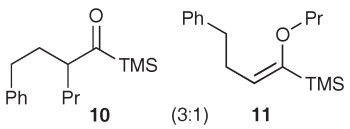
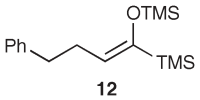
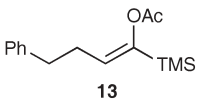
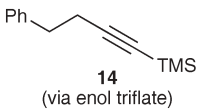
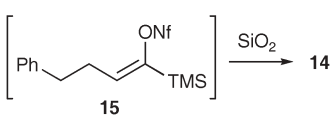
product could not be detected by ^{1}H NMR spectroscopy). Allowing the reaction to warm to −37 °C afforded the [1,2] and [1,4] products **2** and **3** in a combined 83% yield and 9:1 ratio in favor of the [1,4] product. However, at room temperature, the [1,4]:[1,2] selectivity was not improved over MeLi, and the yields were comparable. *s*-BuLi was found to be superior to both *n*-BuLi and MeLi in initiating the Wittig rearrangements of α-alkoxysilanes (results are shown in Table 1). Upon treatment of a cold (−78 °C) THF solution of our model substrate **1** with 1.5 equivalents of *s*-BuLi (1.3 M in cyclohexane), Wittig rearrangement was complete in 30 min to afford the [1,4]-rearrangement product **2** exclusively[12] and in good yield (79–83%).[13,14] To the best of our knowledge, this is the most rapid, selective, and efficient [1,4]-Wittig rearrangement of α-alkoxysilanes in particular, and allyl benzyl ethers in general, to be reported.

We believe these data suggest different mechanisms for the [1,4]- and [1,2]-rearrangements of **1**. Previous studies on the concerted [2,3]-Wittig determined that the stepwise [1,2]-Wittig becomes competitive at higher temperatures.[1] Thus, if concerted, a [1,4]-reorganization should be preferred at cold temperatures, provided the base is strong enough to deprotonate the starting material (*e.g.* *s*-BuLi). Entries 3–6 of Table 1 are consistent with this hypothesis. Depending on what base was employed, deprotonation and rearrangement occurred to different extents over each experiment's temperature range. With weaker bases (MeLi and *n*-BuLi) complete deprotonation–rearrangement only occurred after reaction temperatures reached their upper limits and thus more [1,2]-Wittig was seen. In contrast, *s*-BuLi deprotonated **1** at the lower end of the temperature range thereby allowing the [1,4]-Wittig to proceed nearly unopposed.

Table 2 1,4-Wittig rearrangement–enolate trapping



Entry	Electrophile	Product(s)	Yield (%)
1	CH_2=$CHCH_2Br$	 **5**	55
2	$PhCH_2Br$	 **6**	66
3	MeI	 **7**	73
4	EtI	 **8** (3:1) **9**	81
5	PrI	 **10** (3:1) **11**	66
6	PhCHO	Over condensation	—
7	TMSCl	 **12**	73
8	AcCl	 **13**	69
9	$PhNTf_2$	 **14** (via enol triflate)	58
10	$CF_3(CF_2)_2SO_2F$	 **15**	58

Having established highly selective [1,4]-Wittig conditions, we next sought to take advantage of the enolate generated upon rearrangement by quenching the reaction with various electrophiles (Table 2).[15] This would establish the [1,4]-Wittig as a new way to build α-substituted acylsilanes.

As such a protocol would involve C–C bond forming reactions at both the γ- and α-carbons of the final product, the reaction sequence would represent an alternative to the conjugate addition of nucleophiles to 1-trimethylsilylpropenone followed by electrophile capture as a means of synthesizing these TMS-ketones. Curiously enough, to the best of our knowledge, such an approach to elaborating α,β-unsaturated acylsilanes has been used only in a handful of specialized cases.[16] As such the route described herein appears to be unprecedented in its generality.

The results of our trapping experiments are summarized in Table 2.[17] Allylation, benzylation, and methylation afforded only α-*C*-alkylated acylsilanes (**5–7**) in moderate to good yields (Table 2, entries 1–3). Reaction with ethyl iodide or propyl iodide resulted in 3:1 mixtures of the *C*- and *O*-alkylated products (81% and 66% yields respectively) (entries 4–5). Benzaldehyde proved a troublesome electrophile as over condensation was difficult to control (entry 6).[18] However, quenching with TMSCl selectively gave (*E*)-*O*-silylenol ether **12** in 73% yield (entry 7).[19] In light of the benzaldehyde result, the efficient generation of the silylketene acetal is noteworthy since such compounds react well under Mukaiyama aldol conditions to give β-alkoxyacylsilanes.[20] Similarly, enol ester **13**,[19] resulting from the reaction with Ac_2O, could also be obtained by this protocol (entry 8).

This process could also be used as a route to TMS-substituted alkynes. As discovered by Fleming and Mwaniki, enol triflates of acylsilanes are prone to rapid dehydration.[21] Thus trapping with $PhNTf_2$ did not afford any observable amounts of the corresponding vinyl triflate, but rather gave trimethyl(4-phenylbut-1-ynyl)-silane **14** in 58% yield (entry 9). Use of the nonaflating reagent $CF_3(CF_2)_3SO_2F$ under similar reaction conditions resulted in the formation of the vinyl nonaflate **15** as determined from the ^{1}H NMR spectrum of the crude reaction mixture. However, even the nonaflate proved sensitive to acidic conditions and, once subjected

to silica gel column chromatography, it too underwent elimination to give **14** in the same 58% isolated yield (entry 10).

In summary, we have established that, upon deprotonation with *s*-BuLi, α-benzyloxyallylsilane (**1**) undergoes [1,4]-Wittig rearrangement with unprecedented selectivity. By concluding the reaction with the addition of an electrophile, α-benzyloxyallylsilane serves as a unique source of a variety of α-substituted acylsilanes.

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Notes and references

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6 (*a*) R. E. Maleczka, Jr. and F. Geng, *Org. Lett.*, 1999, **1**, 1115–1118; (*b*) for the preparation of **1** see: ref. 2*d*.

7 In ref. 6*a*, we mistakenly assigned **3** as a [2,3]-Wittig derived product. In actuality, this product is the result of a [1,2]-Wittig followed by migration of the TMS group to the β-carbon. If this migration is the result of a direct [1,3]-shift or involves a Brook/vinylogous retro-Brook rearrangement is unclear at this time (also see ref. 5*j*).

8 (*a*) A. E. Mattson and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 4363–4366; (*b*) A. E. Mattson, A. R. Bharadwaj and K. A. Scheidt, *J. Am. Chem. Soc.*, 2004, **126**, 2314–2315.

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12 [1,2]-Wittig product **3** was not detected (by TLC, ^{1}H NMR or GC-MS).

13 Wittig rearrangement of compound **1**: a solution of 76 mg (0.34 mmol) of α-alkoxysilane **1** in 4.5 mL of freshly distilled dry THF, was cooled to −78 °C under N_2. *s*-BuLi (1.3 M in cyclohexane, 0.4 mL, 0.52 mmol, 1.5 equiv.) was added dropwise *via* syringe. The reaction mixture was stirred for 30 min at −78 °C and then quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, and subsequently washed with H_2O and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (0–2% EtOAc–hexane gradient) afforded 63 mg (82%) of acylsilane **2** as a light yellow oil. IR (neat) 2955, 1717, 1643, 1497, 1454, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.17 (m, 5H), 2.62–2.59 (overlapping dd, J = 7.3, 6.8 Hz, 2H), 2.58–2.55 (overlapping dd, J = 7.8, 7.3 Hz, 2H), 1.87–1.81 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.1, 141.8, 128.4, 128.3, 125.8, 47.5, 35.2, 23.6, −3.2. HRMS (EI) *m*/*z* 219.1210 [(M − H)$^+$; calcd for $C_{13}H_{19}OSi$ 219.1210].

14 For alternative preparations of **2** see: (*a*) N. G. Bhat, A. Tamm and A. Gorena, *Synlett*, 2004, 297–298; (*b*) C. Hammaecher, I. Ouzzane, C. Portella and J.-P. Bouillon, *Tetrahedron*, 2005, **61**, 657–663.

15 Enolate **4** had been trapped previously with allyl bromide to afford α-allyl acylsilane **5** in 15% yield. F. Geng, PhD thesis, Michigan State University, 2001.

16 (*a*) α,β-Unsaturated silylketones have been reported to undergo conjugate additions with cuprates, however no details of these reactions were described in: H. J. Reich, M. J. Kelley, R. E. Olson and R. C. Holtan, *Tetrahedron*, 1983, **39**, 949–960. For annulations with allenylsilanes see: (*b*) R. L. Danheiser and D. M. Fink, *Tetrahedron Lett.*, 1985, **26**, 2513–2516. For cyclopropanations see: (*c*) J. S. Nowick and R. L. Danheiser, *Tetrahedron*, 1988, **44**, 4113–4134. For examples of 1,4-additions with TMS-substituted nucleophiles see: (*d*) A. Ricci, A. Degl'Innocenti, G. Borselli and G. Reginato, *Tetrahedron Lett.*, 1987, **28**, 4093–4096; (*e*) A. Degl'Innocenti, P. Ulivi, A. Capperucci, G. Reginato, A. Mordini and A. Ricci, *Synlett*, 1992, 883–886. Also see: (*f*) I. A. Stergiades and M. A. Tius, *J. Org. Chem.*, 1999, **64**, 7547–7551.

17 Electrophilic trapping of enolate **5**: the Wittig rearrangement was carried out as described above (ref. 13). Upon complete rearrangement (*ca.* 30 min. at −78 °C), the resultant enolate solution was transferred *via* cannula to a THF solution of the electrophile at the indicated temperature (Table 2). The reaction was then stirred for the indicated time with monitoring by TLC. The mixture was then quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. Phases were separated and the organic phase washed with H_2O and brine. Workup was then carried out as described above to afford the α-substituted acylsilane.

18 NMR and HRMS analysis suggest two molecules of benzaldehyde are incorporated in the product, but the exact structure of this compound is unclear.

19 The *E* geometries of the both **12** and **13** were based on the spectral data for **13** being identical to those previously reported for that geometric isomer. See: M. Yamane, K. Uera and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 477–486.

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