Hydroalumination

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γ-Silyl Group Effect in Hydroalumination and Carbolithiation of Propargylic Alcohols[**]

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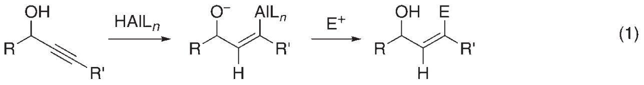
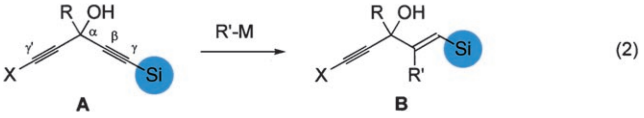
The hydrometalation reaction of an alkynyl group is a valuable process, not only for functionalized alkene synthesis but also for alkenyl metal preparations.[1] Among the numerous variants of this class of reaction, hydroalumination of propargylic alcohols is especially well utilized in many facets of organic synthesis owing to its promising chemo- and stereoselectivity [Eq. (1); L = ligand, E = electrophile].[2,3]

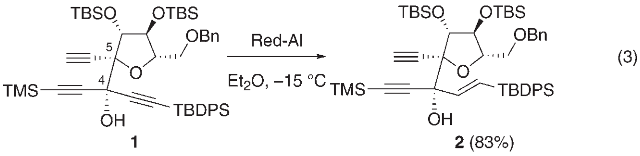


Herein, we report a noticeable accelerating effect of a γ-silyl substituent on the hydroalumination reaction, an effect that can substantially enhance the synthetic utility of this classical transformation. By proper choice of the silyl group, highly group-selective functionalization in polyalkynyl alcohols **A** has been accomplished by overcoming the steric influences, to provide valuable multifunctionalized alcohols **B** through hydroalumination and also carbolithiation [Eq. (2)].



R = H, alkyl, alkynyl; X = alkyl, SiR''$_3$
R' = H, alkyl; M = Al, Li

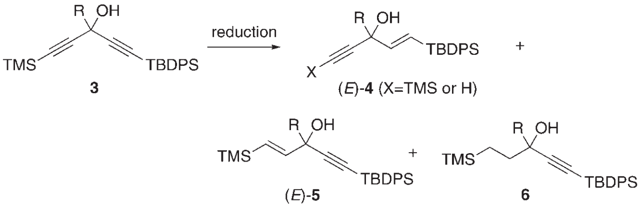
We have found this unprecedented silyl effect during the course of our synthetic study of zaragozic acid A.[4] As one of the key steps in this total synthesis, we faced the problem of group-selective functionalization of intermediate **1**, which has three alkynyl groups on C4 and C5 [Eq. (3); Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl]. Surprisingly enough, hydroalumination of alcohol **1** with sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) provides vinylsilane **2** exclusively.[5]



Our purpose for the total synthesis was achieved by this group-selective transformation; however, a question that immediately arose was why the reaction preferentially occurred at the alkyne substituted with the bulkier TBDPS group, rather than one substituted with the less bulky TMS group.[6] At an earlier stage, we suspected an influence of the multiple oxy functionalities on **1** to be the origin of the peculiar selectivity; these functionalities may exert chelation control on the aluminum reagent.[7] Thus, in order to eliminate this confusing factor, we examined a competitive hydroalumination in a series of simplified 1,1-bis(alkynyl) alcohols **3** bearing TBDPS and TMS groups at the γ and γ' positions (Table 1).

The reaction of *sec*-alcohol **3a** (R = H) with Red-Al in toluene at 0 °C provides vinylsilane (*E*)-**4a** (95 %) predominantly, along with a trace amount of (*E*)-**5a** (3 %; TBDPS side/TMS side 97:3; Table 1, entry 1).[8] Similar selectivity was

Table 1: Reduction of 1,1-bis(alkynyl) alcohol **3**.



Entry	3	R	Reagent (equiv)	Solvent, *T*	Yield [%][a]			TBPS side/ TMS side
					4[b]	**5**[b]	**6**	**4**/(**5**+**6**)
1	**3a**	H	Red-Al (1.1)	toluene, 0 °C	95[c]	3	n.d.[d]	97:3
2	**3a**	H	$LiAlH_4$ (3.0)	THF, −78 to −10 °C[e]	58[c]	6	n.d.[d]	91:9
3	**3b**	Me	Red-Al (1.1)	toluene, 0 °C	88	5	n.d.[d]	95:5
4	**3b**	Me	H_2, Lindlar cat. (0.11)	MeOH, RT	n.d.[d]	70[f]	19	< 1:99

[a] Yield of isolated product. [b] > 95 % *E* by ^{1}H NMR analysis. [c] The product with the TMS group removed (X = H) was obtained in 7–16 % yield. [d] n.d. = not detected by ^{1}H NMR and TLC analyses. [e] THF = tetrahydrofuran. [f] The *E*/*Z* ratio was determined by ^{1}H NMR analysis to be 83:17.

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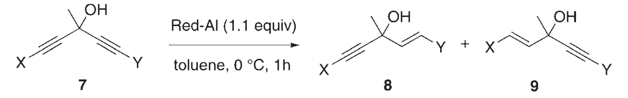
observed when $LiAlH_4$ was employed instead of Red-Al (TBDPS side/TMS side 91:9; entry 2) and also in the reaction of *tert*-alcohol **3b** (TBDPS side/TMS side 95:5; entry 3). From these results, it was clarified that the peculiar selectivity of the reaction of **1** was caused by the γ-silyl group of the propargylic moiety. In sharp contrast with the above-mentioned hydroalumination, a partial reduction of **3b** by catalytic hydrogenation (H_2/Lindlar catalyst) preferentially gave product **5b**, from reduction of the less-hindered TMS-substituted alkyne, and the overreduced product **6b** (TBDPS side/TMS side <1:99; entry 4). These results obviously show that the TBDPS substituent, rather than the TMS group, accelerates hydroalumination on the attached ethyne functionality, despite its steric disadvantage. A stereoelectronic effect of the phenyl group on silicon (see below) is regarded as the origin of this TBDPS effect. Based on this postulate, we anticipated that a triphenylsilyl group (TPS) would have a much higher ability to accelerate hydroalumination than that of TBDPS. To confirm this idea and to determine the order of magnitude of the rate acceleration by various substituents, we examined the competitive hydroalumination of 1,1-bis(alkynyl) alcohols **7a–g**, which have various combinations of γ substituents; the results are summarized in Table 2.[8]

Table 2: Hydroalumination of 1,1-bis(alkynyl) alcohol **7**.



Entry	**7**	X	Y	Yield (**8**+**9**) [%][a]	**8/9**[b]
1	**7a**	*t*Bu	TMS	91	>99:1
2	**7b**	TMS	TIPS[c]	97	55:45
3	**7c**	TIPS[c]	TBDPS	100	88:12
4	**7d**	TBDPS	TPS	93	72:28
5	**7e**	TMS	Ph	89	94:6
6	**7f**	TBDPS	Ph	40[d]	55:45
7	**7g**	Ph	TPS	79	78:22

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis. [c] TIPS = triisopropylsilyl. [d] 1,1-Bis(alkenyl) alcohol (doubly reduced product) was obtained as a byproduct in 18% yield.

As can be seen from the results of **7a** and **7e** (Table 2, entries 1 and 5), the acceleration effect of TMS is higher than that of the alkyl group, but lower than that of the phenyl group.[9] Among the examined substituents, the TPS group shows the highest aptitude, as we expected (see results for **7d** and **7g**; entries 4 and 7). From these results, the order of the magnitude of the rate enhancement was determined to be: TPS > Ph ≈ TBDPS > TIPS ≈ TMS ≫ alkyl. Thus, the observed significant acceleration effect of TBDPS and TPS is explainable by the increase of electrophilicity of the β-carbon atom on the alkynyl group caused by the phenyl groups on the silicon atom. The alkynyl group acts as an electrophile (hydride acceptor) in a hydroalumination with an aluminum ate complex,[2a,3i] and the phenyl groups on the TBDPS and TPS moieties should raise the electrophilicity of the ethyne due to a hyperconjugation of the phenyl and ethyne π orbitals through a Si–C σ* bond.[10] This supposition was well supported by DFT calculations of the simple TPS- or TBDPS-substituted propargyl alcohols **10** and **11**, in which the lowest unoccupied molecular orbital (LUMO) of the alcohol consists of the π* orbital of the phenyl groups, the σ* orbital of the Si–C bond, and the π* orbital of the ethyne moieties (Figure 1).[11] The calculated LUMO energy levels of **10** and **11** are significantly lower than that of the TMS-substituted counterpart **12** (**10**: −0.9965 eV, **11**: −0.9954 eV, **12**: −0.4438 eV).[12–15]

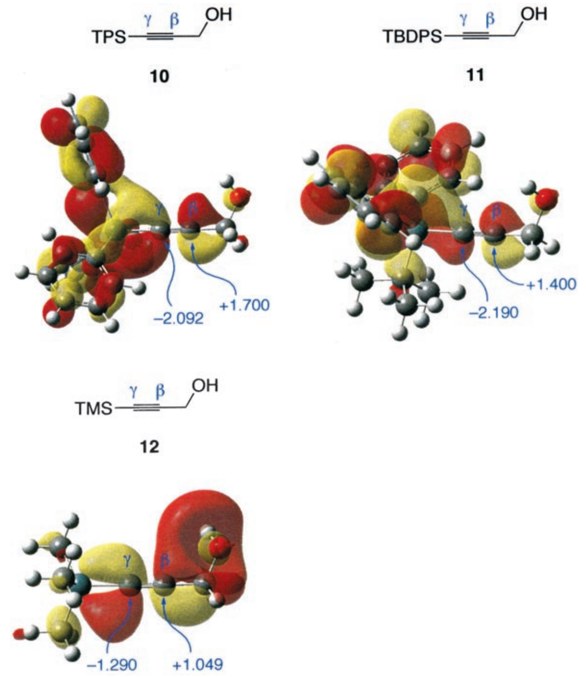
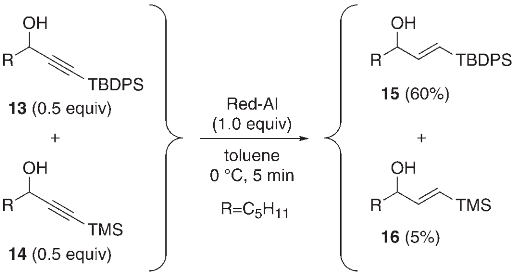


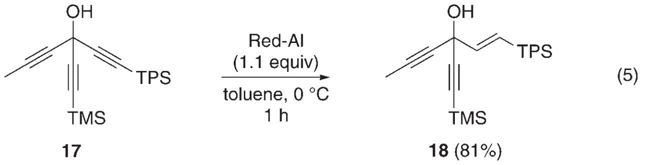
Figure 1. LUMOs of silyl-substituted propargyl alcohols **10–12** and Mulliken charges on the alkyne carbon atoms.

A similar accelerating effect was observed in an intermolecularly competitive variant, in which the reaction of an equimolar mixture of TBDPS- and TMS-substituted propargylic alcohols **13** and **14** with Red-Al gave vinylsilane **15** as the major product after 5 min (TBDPS side/TMS side 92:8) [Eq. (4)].

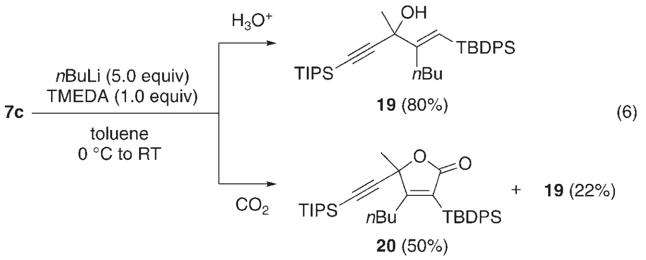


(4)

Moreover, proper combination of silyl groups may also enable group-selective functionalization in 1,1,1-tris(alkynyl)alcohol systems. For instance, the reaction of alcohol **17**, having TPS, TMS, and methyl groups at the γ positions, with Red-Al provided vinylsilane **18** as the sole product in 81% yield [Eq. (5)].



Finally, we examined expansion of this methodology to a carbon–carbon bond-forming reaction, that is, carbolithiation of propargylic alcohol.[16] The reaction of alcohol **7c** with *n*BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) gave allylic alcohol **19**, with a trisubstituted alkene moiety, in 80% yield with excellent group selectivity. The stereochemistry of the resulting alkene was determined as the *E* configuration by transformation to the γ-lactone **20** through CO_2 trapping of vinyl lithium [Eq. (6)].



In summary, we have described a remarkable acceleration effect of phenyl-substituted silyl groups in hydroalumination and carbolithiation reactions of propargylic alcohols. These results clearly show that an arylsilyl group can act not only as a protecting group but also as an activating group of the alkynyl moiety. This work provides an efficient group-selective approach to multifunctionalized alkenes. Further work is underway in our group to expand the utility of this interesting phenomenon.

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Keywords: alkenes · carbolithiation · hydroalumination · hyperconjugation · substituent effects

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[6] The difference in bulkiness between TMS and TBDPS plays an important role in the diastereoselectivity of the [1,2]-Wittig rearrangement which forms a C–C bond between C4 and C5; see ref. [4].

[7] Quite recently, Suzuki's group has developed a chelation-controlled diastereoselective hydroalumination in a 1,1-bis(alkynyl) alcohol system. They performed stereoselective construction of continuous pseudoquaternary chiral centers by using this method; see ref. [3k–m].

[8] The produced alcohols (that is, **4** and **5**) were easily distinguished by ^{1}H and ^{13}C NMR analysis after selective desilylation at the alkyne terminal.

[9] It has been reported that a phenyl substituent increases the electrophilicity of alkynes. For example, Slaugh's group reported that the reaction of diphenylacetylene with $LiAlH_4$ proceeds markedly faster than the same reaction of dialkylacetylene: E. F. Magoon, L. H. Slaugh, *Tetrahedron* **1967**, *23*, 4509–4515.

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[11] It has been reported that hydroalumination of alkynes with an ate-complex aluminum reagent is strongly dependent on the electrophilicity of the alkyne. Kakinuma, Matsuzawa, and Eguchi discussed the relationship between the LUMO level of the alkyne and the reactivity of the propargylic alcohols in hydroalumination with $LiAlH_4$; see ref. [3i].

[12] These calculations were performed at the B3LYP/6–31+G(d)//B3LYP/6–31G(d) level with Gaussian 98.

[13] For more detailed discussion, calculation of a transition-state model is needed.

[14] We have found that measurement of the $\Delta\delta$ value of the ethyne carbon atoms ($\delta_{\beta\text{-carbon}}-\delta_{\gamma\text{-carbon}}$) in ^{13}C NMR analysis can predict the reactivity of silyl-substituted propargylic alcohols. Actually, the $\Delta\delta$ value of **10** was higher than that of the less reactive one (**10**: 22.4; **11**: 21.8; **12**: 13.1), which means that the $\Delta\delta$ value shows a polarization of the ethyne carbon atoms and electrodeficiency on the β-carbon atom.

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