

Reactivity Studies of 3,3-Bis(trimethylsilyl)-2-methyl-1-propene in Lewis Acid-Catalyzed Allylation Reactions

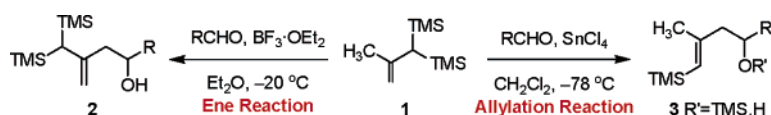
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ABSTRACT



Allylation reagents, which possess geminal bis-trimethylsilyl substitution, are readily prepared from *E*- or *Z*-alkenyl bromides. The reactivity of 3,3-bis(trimethylsilyl)-2-methyl-1-propene (1) is described and predominantly provides ene reactions with aldehydes to give alcohol 2 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. Alternatively, Sakurai allylation reactions of 1 are observed by using stronger Lewis acids in methylene chloride to exclusively yield *E*-trisubstituted alkenylsilanes 3.

Allylation reactions have proven to be among the most widely utilized techniques for the synthesis of complex molecules.¹ A variety of methods allow for optimization of stereo- and regiocontrol in the formation of homoallylic alcohols.² Our investigations toward the synthesis of natural products have led to the development of reagents for allylations which facilitate subsequent cross-coupling processes.³ In this fashion, the allyl nucleophile serves as a lynchpin for bi-directional construction, using general reactions with widespread implications for synthetic design. The generality of this concept is illustrated by the allylation of bis-trimethylsilylpropene 4 yielding the vinylsilane 5 for electrophilic replacement as shown in alcohol 6 (Figure 1).

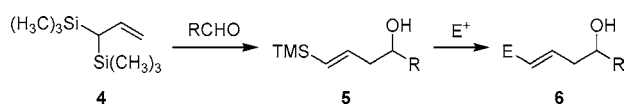


Figure 1. Bi-directional construction via allylation.

Studies of 3,3-bimetallic allyl species⁴ have described the formation of various stannyl derivatives⁵ and Marshall has

documented the general reactivity and the ease of 1,3-isomerizations of these substances to yield the corresponding 1,3-bimetallic compounds.⁶ Pornet and co-workers⁷ have reported the preparation of 3,3-bis(trimethylsilyl)-1-propene via the controlled hydrogenation of 1,1-bis(trimethylsilyl)-prop-2-yne as well as subsequent allylation reactions with aldehydes in the presence of titanium tetrachloride. In this letter, we report a general method that permits the synthesis of 3,3-bis(trimethylsilyl)-1-propenes with control of alkene geometry. Investigations of the chemical behavior of 3,3-bis(trimethylsilyl)-2-methyl-1-propene have led to findings of Lewis acid-catalyzed ene reactions as well as conditions

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which promote the anticipated allylation reactions. These results illustrate the potential of 3,3-bis(trimethylsilyl)-2-methyl-1-propene as a lynchpin for bi-directional synthesis via allylation processes which provide for subsequent silyl substitution strategies.

Efficient preparation of bis(trimethylsilyl) allyl species is carried out in a single step via the Kumada⁸ coupling of an alkenyl bromide and bis(trimethylsilyl)methylmagnesium chloride.⁹ Table 1 summarizes results of the cross-coupling

Table 1. Syntheses of Bis(trimethylsilyl)-2-alkenes

alkene 8	product 9	isolated yield (%)
1		87
2		88
3		70
4		87
5		83
6		83
7		35

reactions of the Grignard reagent **7** with alkenyl bromides in the presence of Pd(PPh₃)₄. Reactions proceed at 40 °C within 14 to 20 h with excellent yields of desired product **9** and retention of olefin geometry. As expected, *E*-alkenyl bromide (entry 2) reacts faster than the corresponding *Z*-isomer (entry 3). Bis(trimethylsilyl) products **9** are isolated following flash chromatography and can be stored for several months (−20 °C). This procedure was applied to the preparation of **1** on a multigram (10 g) scale without compromising the overall efficiency of the reaction.

Studies of target-oriented natural product synthesis have led us to examine the allylation reactivity of 3,3-bis(trimethylsilyl)-2-methyl-1-propene (**1**) with a variety of aldehydes. Our initial attempts displayed products of an ene

Table 2. Ene Reactions of 3,3-Bis(trimethylsilyl)-2-methyl-1-propene (**1**) and Aldehydes

aldehyde ^(a)	product	ratio ^(b) 10 : 11	yield of 10 ^(c)
1		12:1	66%
2		9:1	60%
3		14:1	56%
4		19:1 dr >20:1 ^(d)	59%
5		8:1 dr >20:1 ^(d)	57%
6		19:1	48%
7		10:1	46%
8		3:1	46%
9		12:1 dr >20:1 ^(d)	47%
10		6:1 dr 2:1 ^(d)	44%

^a Standardized conditions are not optimized for each aldehyde. Reactions are quenched by addition of aq NaHCO₃ at −20 °C. ^b Ratios of **10:11** were determined from ¹H NMR data of crude reaction product. ^c Isolated yields of **10** follow flash chromatography. Products were fully characterized after purification. ^d Diastereoselectivity (dr) was determined from ¹H NMR data.

reaction, thus retaining the bis(trimethylsilyl) moiety. Indeed, the propensity of the methallyl unit to display ene reactivity has been reported for reactions of trimethylmethallylsilane with methyl glyoxylate,¹⁰ and ene-carbonyl additions of methallylsilanes and 3-phenylpropionaldehyde with organoaluminum catalysis have been communicated.¹¹ Markó and co-workers¹² have described ene reactions of derivatives of 2-trimethylsilylmethyl-2-propen-1-ol and selective formation of TBS silyl enol ethers.¹³ These enolic products undergo

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(12) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595.

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Table 3. Sakurai Allylation of Aldehydes with 3,3-Bis(trimethylsilyl)-2-methyl-1-propene (**1**)

	aldehyde ^(a)	major product	ratio ^(c) 11 : 10	yield of 11 ^(d)
1			>25:1	82%
2			>25:1	76%
3			>19:1	56%
4			10:1 dr 2.5:1 ^(e)	57%
5			2:1 dr >20:1 ^(e)	29%
6			>25:1	79%
7			>19:1 ^(b)	76%
8			>19:1 ^(b)	73%
9			>19:1 dr >20:1 ^(c)	62%
10			5:1 dr >20:1 ^(e)	61%
11			>25:1 ^(b)	75%

^a Standardized conditions are not optimized for each aldehyde substrate.

^b Entries 7, 8, and 11 were quenched with NEt_3 at -78°C instead of MeOH.

^c Ratios of **11**:**10** were determined from ^1H NMR data of crude reaction product. ^d Isolated yields of **11** follow flash chromatography. Products were fully characterized after purification. ^e Diastereoselectivity (dr) was determined from ^1H NMR data.

facile intramolecular Sakurai cyclizations.¹⁴ By comparison, reagent **1** is designed with geminal TMS substituents to provide an anticipated bias for allylation. In fact surprising chemoselectivity for the ene process is observed without regard for the structure or the reactivity of the aldehyde

(14) Markó, I. E.; Dumeunier, R.; Leclercq, C.; Leroy, B.; Plancher, J. M.; Mekhalfia, A.; Bayston, D. J. *Synthesis* **2002**, 7, 958.

component when $\text{BF}_3\cdot\text{OEt}_2$ is used as the Lewis acid catalyst. Table 2 summarizes our results for ene reactions of **1** under these conditions. In most cases, small amounts (3% to 12%) of competing Sakurai allylation products are observed. Flash chromatography has provided purification and characterization of each of the homoallylic alcohols **10**. Our interest in reactions of aldehydes which incorporate an alkoxy substituent is summarized by entries 4, 5, 9, and 10. Excellent stereoselectivity for the formation of the Felkin-Ahn product is obtained (dr >20:1) with the exception of the α -benzyloxy aldehyde of entry 10, Table 2 (dr 2:1).¹⁵ Unfortunately, electron-rich aromatic aldehydes and α,β -unsaturated aldehydes have shown poor reactivity under these conditions.

We have also examined the Sakurai allylations of **1** which are favored by the use of stronger Lewis acids in methylene chloride. SnCl_4 was generally found to be an effective catalyst for allylation under standardized conditions at -78°C . Table 3 provides a compilation of results. In most cases (entries 1, 2, 6, and 11), ene product is not detected by ^1H NMR spectroscopy whereas entries 4, 5, and 10 demonstrate reduced chemoselectivity. On the other hand, we have not observed olefinic products which would arise from 1,3-bis-stannylated intermediates derived via preliminary allylic transposition from **1**.⁶ Aldehydes containing α -alkoxy substitution yield syn products via chelation-controlled addition.¹⁵ Entry 4 gave a mixture of syn and anti alcohols (dr 2.5:1). In all examples, the *E*-trisubstituted silane is exclusively formed¹⁶ and provides a reactive site for further chemistry.

We have considered the feasibility of two open transition states to account for the formation of *E*-alkenylsilanes. As shown in Figure 2, minimization of allylic strain and

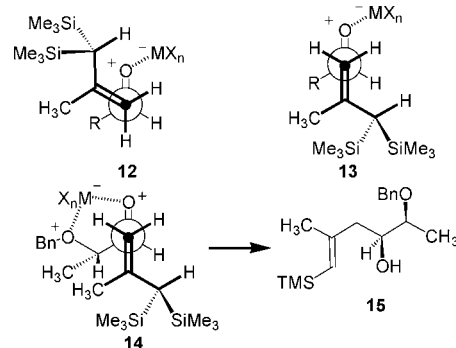


Figure 2. Synclinal and antiperiplanar arrangements leading to **11** (M = Sn, X = Cl).

nonbonded interactions leads to the synclinal arrangement **12** and antiperiplanar **13**. While either of these possibilities

(15) The stereochemistry of optically active alcohols for entries 5 and 10 was resolved by modified Mosher ester analysis (Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, 30, 3147). Relative stereochemistry of syn and anti products was assigned by comparison with literature results (Ciufolini, M. A.; Deaton, M. V.; Zhu, S.; Chen, M. *Tetrahedron* **1997**, 53, 16299). Relative stereochemistry of products of entries 4 and 9 was confirmed by chemical synthesis, see the Supporting Information.

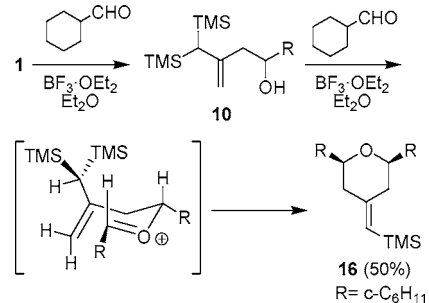
delivers the *E*-olefin geometry, it has been observed that reactions quenched with anhydrous NEt_3 at $-78\text{ }^\circ\text{C}$ yield the corresponding trimethylsilyl ethers (entries 7, 8, and 11; Table 3). These results lead to speculation regarding the internal transfer of TMS to oxygen in synclinal **12**.¹⁷ On the other hand, intermolecular silyl transfer may be promoted by a reactive ammonium species. Additional insight is gained from the reactions of α -alkoxyaldehydes. In these examples the antiperiplanar approach minimizes steric interactions leading to syn stereochemistry in **15** via chelation-controlled addition as depicted in **14**.

An alternative explanation for formation of *E*-alkenylsilanes **11** would suggest that initial ene products **10** are subsequently transformed via protodesilylation with allylic transposition. In support of this rationale, we have noted that ene reactions (Table 2, entry 1) quenched at 25% conversion (30 min at $-20\text{ }^\circ\text{C}$) provide a 19:1 ratio of ene product **10** to **11**. Longer reaction times (2 h), leading to reaction completion, indicate an erosion of **10**:**11** product ratio (12:1). To probe this possibility, ene product **10** (derived from Table 2, entry 1) was dissolved in ether and cooled to $-20\text{ }^\circ\text{C}$ under nitrogen. Precooled $\text{BF}_3\cdot\text{OEt}_2$ in ether was added, and after stirring (2 h), the reaction was quenched in the usual way (aq NaHCO_3 at $-20\text{ }^\circ\text{C}$). This procedure led to recover **10** with the observation of 5% or less of the acid-catalyzed conversion to **11** (product ratio $>19:1$). These efforts support the hypothesis of a dominant ene reaction directly competing with a less favorable silyl-allylation process. The secondary isomerization pathway of **10** to the *E*-alkenylsilane **11** is also operating. Related experiments with SnCl_4 in methylene chloride at $-78\text{ }^\circ\text{C}$ were stymied by the fast reaction times encountered under these conditions. In addition, treatment of **10** with TsOH in methylene chloride at $0\text{ }^\circ\text{C}$ immediately leads to an equal mixture of *E*- and *Z*-alkenylsilanes as well as the terminal olefin arising from complete protodesilylation.

Preliminary studies have demonstrated the one-pot, sequential ene and Sakurai allylation from **1** by incorporation of two aldehyde components, providing 2,6-*cis*-disubstituted

tetrahydropyrans with an exocyclic alkenylsilane (Scheme 1).^{14,18} Thus, cyclohexane carboxaldehyde (2 equiv) leads

Scheme 1. Tandem Ene–Allylation Cyclization



directly to pyran **16** (50% yield) in ether at $-20\text{ }^\circ\text{C}$.

In summary, a highly efficient procedure provides preparation of geminal 3,3-bis(trimethylsilyl)-1-propenes with opportunities for control of alkene geometry via a mild palladium-catalyzed cross coupling. A case study of the reactivity of 3,3-bis(trimethylsilyl)-2-methyl-1-propene (**1**) has shown the propensity for ene reactions with $\text{BF}_3\cdot\text{OEt}_2$ in diethyl ether. Alternatively, Sakurai allylations are observed with SnCl_4 in methylene chloride. This dual reactivity permits sequential allylation processes for bi-directional synthesis as well as the potential for further elaboration via cross-coupling reactions.

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Supporting Information Available: Experimental procedures and spectral characterization for compounds **9**, **10**, **11**, and **16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Trisubstituted alkene geometry was determined by 1D-NOE's of the vinylic hydrogen and the allylic methylene hydrogens.

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