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The Preparation and Reactivity of 2-Bromo-3-(tri-*n*-butylstannyl)-1-propene

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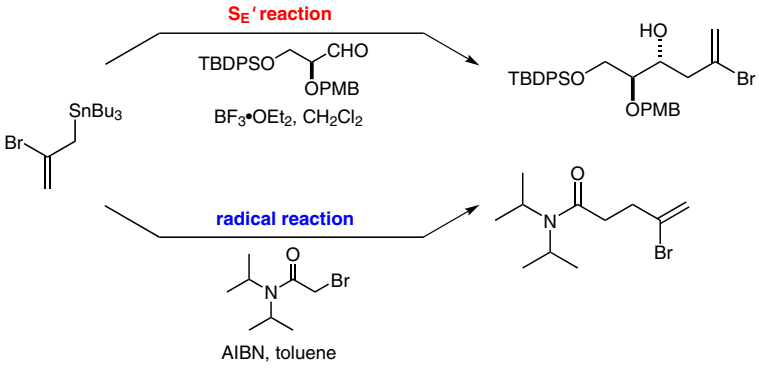

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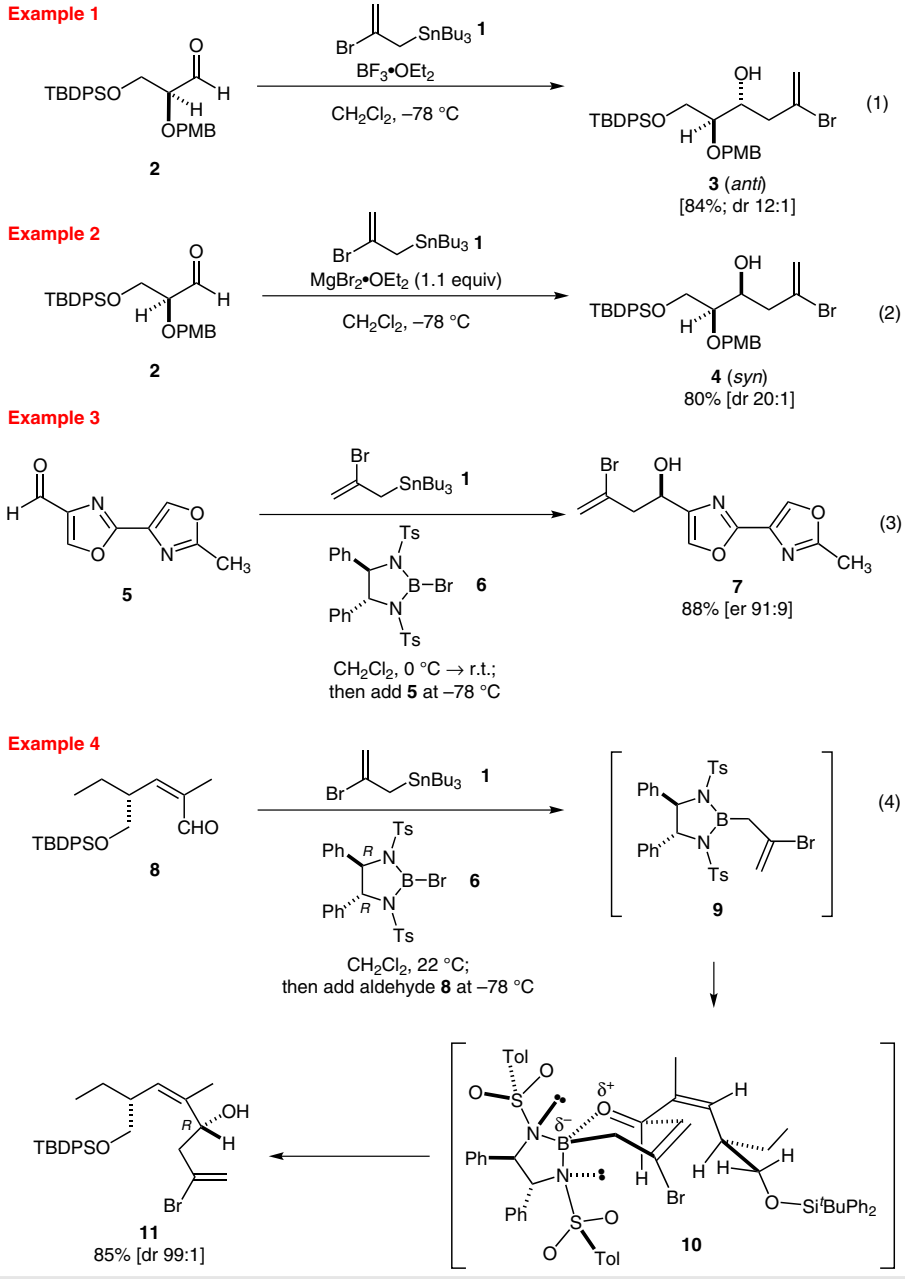
Abstract The preparation of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene is described. This study characterizes the reactivity of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene in S$_E$′ reactions with aldehydes and includes a survey of radical reactions of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene with α-bromocarbonyl compounds for C-alkylation.

Key words organostannane preparation, bifunctional reagent, S$_E$′ reactions, radical reaction, alkenyl bromides

Our studies of natural product synthesis have sought improved strategies for the efficient assembly of molecular complexity by utilizing bifunctional reagents that provide for the sequential execution of high-value reactions.[4] In fact, the design of efficient strategies for total synthesis has provided an important impetus for the creative deployment of bifunctional synthons.[5] We have examined a sequential linkage of asymmetric S$_E$′ reactions and cross-coupling processes to present a versatile strategy for the preparation of complex enantioenriched alcohols.[6,7] In this fashion, bifunctional reagents serve as lynchpins in tandem applications of orthogonal reaction processes. Several contributions have explored this theme, as practitioners have extensively developed a variety of bifunctional allyl synthons to facilitate convergent synthesis pathways.[8] This concept avoids a stepwise construction and the use of protecting groups. In 1989, Corey and co-workers first introduced a protocol for the enantioselective allylation of aldehydes using the 1,2-diamino-1,2-diphenylethane (stien) controller.[9] This initial publication is the first report of 2-bromo-3-tri-*n*-butylstannyl-1-propene (**1**, 2-bromoallyltri-*n*-butyltin) in the literature and its use in asymmetric S$_E$′ reactions. Pulido and co-workers have also described the formation of **1** by a kinetic stannylcupration of allene at –100 °C, and a full account of their study includes characterization data.[10] Subsequently, studies in our laboratories have explored the use of the nonracemic stien controllers in asymmetric S$_E$′ processes,[11] and we have also extended this methodology for total synthesis.[12] Our investigations have utilized 2-bromo-3-(tri-*n*-butylstannyl)-1-propene (**1**),[13] and as a basis for preparation of **1**, we have adapted the general information found in footnote 8 of the original communication (see ref. 9a). We have frequently received requests for a detailed experimental procedure for the preparation and handling of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene (**1**). In this communication, we have summarized the reactivity of **1** in S$_E$′ reactions with aldehydes to effect stereocontrolled formation of homoallylic alcohols, and we have reported new results of a survey of the radical reactions of **1** with α-bromocarbonyl compounds. Most significantly, this communication provides detailed experimental descriptions for two procedures leading to the preparation, the characterization, and the handling of this reactive reagent.

Bifunctional reagent **1** is exceptionally reactive in S$_E$′ substitution processes in which electrophilic attack leads to destannylation with allylic transposition. It is well-known that aldehydes efficiently undergo these reactions at –78 °C in the presence of a Lewis acid catalyst as shown in Scheme 1. Four examples are highlighted from our prior efforts to illustrate typical conditions leading to stereocontrolled reactions using stannane **1**. Homoallylic alcohols are produced as exemplified by the formation of **3** from the chiral nonracemic aldehyde **2**. In this example, the use of BF$_3$·OEt$_2$ results in the diastereoselective synthesis of **3** as predicted by the polar Felkin–Anh model. Substrate-controlled reactions are also demonstrated by the precomplexation of the α-alkoxyaldehyde **2** with a divalent cation. This reaction provides efficient formation of the *syn*-alcohol **4** with high diastereoselectivity arising from a chelation-controlled addition (Scheme 1, eq. 2).[13a]

The allylic stannane of **1** also broadly promotes transmetalation. This reactivity is the basis for the exchange of the stannyl residue with boron leading to in situ formation of chiral, nonracemic 1,3-bis(tolylsulfonyl)-4,5-diphenyl-1,3-diaza-2-borolidines. As a result, reagent-controlled asymmetric allylation reactions of **1** with simple aldehydes readily occur at –78 °C. In these cases, the reactive stannane undergoes transmetalation with the chiral, nonracemic bromoborane **6**. As illustrated in Scheme 1, eq. 3, subsequent addition of aldehyde **5** leads to the enantioenriched alcohol **7**. Reactions of the nonracemic 1,3-diaza-2-borolidine intermediate **9** with chiral aldehydes, such as **8** in Scheme 1, eq. 4, can lead to interesting matched and mismatched stereochemical features favoring transition state **10** and produces excellent diastereoselectivity as illustrated with the formation of **11**.[13b] This methodology is robust and has proven to be useful for convergent strategies which stitch together complex molecular subunits containing significant functionality and stereochemistry.[14]

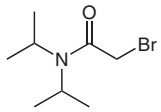
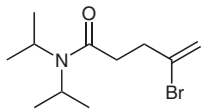
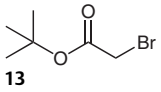
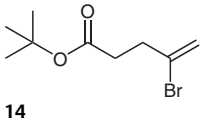
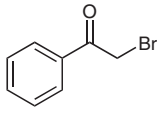
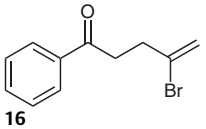
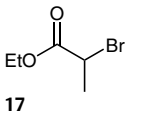
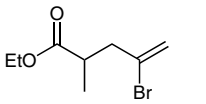
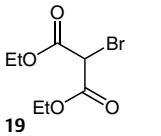
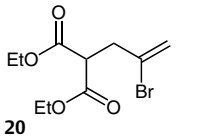
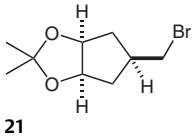
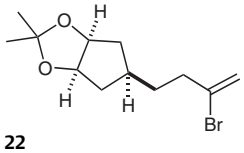
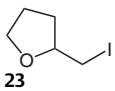
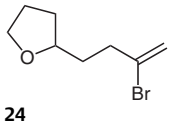


Scheme 1 Examples of S_E' reactions of **1** with aldehydes

Our initial studies of 2-bromo-3-(tri-butylstannyl)-1-propene (**1**) have characterized its radical-mediated reactions with a variety of organic halides to incorporate an alkenyl bromide moiety in C–C bond formation. These findings are presented in Table 1. In this survey, α-bromo carbonyl compounds are preferred substrates. Reactions are conducted in dry toluene under nitrogen atmosphere with gradual heating from 22 °C to 85 °C in the presence of the stannane reagent **1** (2.5–3.5 equiv) and small amounts of AIBN initiator. Generally, α-bromoamides, esters, and ketones are effectively consumed with the formation of alkenyl bromide products (Table 1, entries 1–5) in yields of 61–73%. The corresponding reactions of α-iodo ketones and esters proceed in poor yields, and aryl iodides and bromides are unreactive. Limited studies have probed the use of primary alkyl bromides and iodides and lead to slow reactions with **1** generating modest yields of the desired alkenyl bromides **22** and **24** (Table 1, entries 6 and 7). The rate of the thermal decomposition of stannane **1** becomes a significant factor in these later examples and requires the introduction of an additional aliquot of reagent. With the consumption of 4.5 equivalents of **1**, the products **22** and **24** were produced in yields of 50% and 41%, respectively with the recovery of 15% of the starting halides after three hours at 90 °C. Secondary and tertiary halides did not provide useful yields of the expected products.

The formation of the desired 2-bromo-3-(tri-*n*-butystannyl)-1-propene (**1**)[15] begins with the preparation of a solution of tributylstannyllithium as described by published procedures.[16] To a flame-dried flask containing distilled diisopropylamine (12.0 mL, 85.1 mmol) at 0 °C under inert atmosphere, *n*-butyllithium (2.5 M in hexanes, 31.7 mL; 79.0 mmol) is added dropwise with stirring. Lithium diisopropylamide is formed as a white precipitate, and volatile hexanes and excess amine are then removed in vacuo. Anhydrous THF (143 mL) is then carefully introduced as the reaction flask is maintained at 0 °C under argon. Tri-*n*-butylstannane (21.3 mL, 79.0 mmol) is added dropwise via syringe, and the mixture is stirred for an additional 40 min at 0 °C. The reaction mixture is subsequently cooled to –78 °C, and pre-dried CuBr·DMS (16.25 g, 79.0 mmol) is quickly added as a solid in one portion. During this process, the reaction flask is wrapped with aluminum foil to protect the contents from light, and the reaction mixture becomes an opaque greenish brown in color. This mixture is stirred under argon and protected from light for 2 h at –78 °C. Subsequently, a solution of the methanesulfonate (13.0 g, 60.7 mmol), derived from 2-bromo-1-propen-3-ol,[17] in 20 mL of dry THF is introduced by dropwise addition at –78 °C, and the reaction is allowed to warm to 0 °C with further stirring for 3 h at 0 °C. TLC (20% EtOAc in hexanes) indicates the disappearance of starting mesylate and the formation of desired product (R_f = 0.75). The reaction is quenched by the addition of pH 7 buffer (200 mL), and this mixture is filtered through a Buchner funnel using small amounts of pentane. The filtrate is separated into two phases in a separatory funnel and the aqueous layer is washed with pentane (3 × 150 mL). The combined organic phases are dried over anhydrous Na_2SO_4 and neutralized charcoal, and then filtered through a pad of Celite®. The resulting colorless solution is protected from light and concentrated under reduced pressure while maintaining the bath temperature at approximately 20 °C. Further removal of small amounts of

Table 1 Radical Reactions of Reagent **1** with Reactive Halides[a]

Entry	Starting halide	Product (Yield)[b]	Yield (%)[b]
1	 **11**	 **12**	73%
2	 **13**	 **14**	61%
3	 **15**	 **16**	71%
4	 **17**	 **18**	68%
5	 **19**	 **20**	64%
6	 **21**	 **22**	50%[c]
7	 **23**	 **24**	41%[c]

[a] Stannane **1**, prepared as described, was introduced by syringe as a neat liquid (220 mg, 3.1 equiv, based on 80% purity of **1** from ^{1}H NMR analysis) into a 1 M solution of aldehyde (0.14 mmol) in dry toluene. Several crystals of AIBN were added, and reactions were gradually heated to 85 °C under N_2.
[b] Products were purified by flash silica gel chromatography and were characterized by ^{1}H NMR and ^{13}C NMR analysis. Yields are based on isolated products.
[c] Yields of **22** and **24** were 62% brsm and 52% brsm as starting aldehyde (15%) was recovered in these examples.

solvents under high vacuum gave a colorless to slightly yellow oil. The crude product represents 80–89% of the theoretical mass recovery. This material is evaluated by ^{1}H NMR and ^{13}C NMR analysis to assess its purity. ^{1}H NMR spectroscopy shows signals for two vinylic hydrogens (δ = 5.25 and 5.00 ppm) as well as the allylic methylene of **1** (δ = 2.32 ppm, Figure 1). Evidence for the presence of small amounts (4% or less) of *n*-Bu_3SnH is based upon the characteristic ^{1}H NMR signal (δ = 4.64 (Sn–H) ppm). The major impurity has been identified as hexabutylditin ($Bu_3SnSnBu_3$),[18] which is estimated as 10–15% of the crude product using GC–HRMS with chemical ionization employing isobutane. Unfortunately, both low-resolution MS and various HRMS techniques have failed to provide the confirming identification of a molecular ion signal for **1**. Mass fragments of tri-*n*-butylstannyl and tri-*n*-butyltin bromide are observed. Using the relative integration of vinylic, allylic, and tri-*n*-butyl signals in the ^{1}H NMR data, the estimated purity of crude reaction product is determined to be 80–85% of the desired 2-bromo-3-(tri-*n*-butylstannyl)-1-propene (**1**), based on the presence of hexabutyl ditin. Thus, the calculated yield of **1** is 65–70%, and this material is used directly for subsequent reactions. Yields deteriorate without the use of high quality CuBr·DMS and freshly distilled tri-*n*-butylstannane. Small amounts of the crude product have been distilled by the Kugelrohr bulb-to-bulb transfer technique (oven temperature of 68–72 °C at 1.2 mmHg pressure). However, the colorless distillate is evaluated as desired **1** (approximately 85% pure) containing small quantities of unknown impurities which appear as a result of the distillation (see Supporting Information).

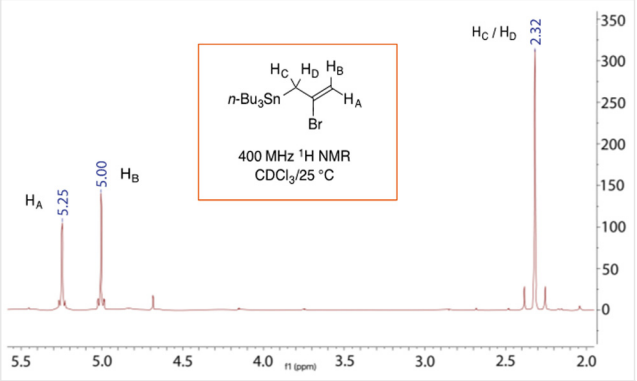


Figure 1 ^{1}H NMR spectrum of **1** for the region δ = 2.0–5.5 ppm illustrates vinylic and allylic hydrogen signal patterns, including observed Sn satellites

Our studies for the preparation of **1** have also examined a second method which utilizes hexabutylditin and commercially available 2,3-dibromopropene while avoiding the use of tri-*n*-butylstannane. For this procedure, lithium wire (1.04 g, 150.0 mmol) is pressed into a thin strip, cut into small pieces under mineral oil, and added into a flame-dried flask, equipped with a stirring bar and a condenser, under an argon atmosphere. A solution of anhydrous THF (20.0 mL) containing several crystals of naphthalene is degassed three times with argon and then is transferred via cannula for reaction with the lithium pieces to give a dark green solution. Hexabutylditin (7.52 mL, 15.0 mmol) is added dropwise via syringe, and the resulting mixture is heated to 50 °C overnight (10 h). Upon cooling to r.t., the dark brown solution is transferred via a Schlenk filtration through a pad of dry Celite® into a flask containing a suspension of recrystallized CuBr·DMS (6.16 g, 30.0 mmol) in anhydrous THF (30.0 mL) at –78 °C. The mixture is protected from light and is continuously stirred at –78 °C for an additional two hours, becoming an opaque greenish-brown color. Freshly distilled 2,3-dibromopropene (3.88 mL, 30.0 mmol) is added via syringe, and the mixture is allowed to warm to 0 °C over 3 h. The reaction is quenched by addition of pH 7 buffer (100 mL) and the organic layer is separated. The aqueous phase is extracted with pentane (200 mL × 3), and the combined organic phases are washed with sat. aq NaCl (300 mL × 2). The resulting pentane solution is dried over $MgSO_4$ and decolorized by the addition of neutral activated charcoal, followed by filtration through a column of basified silica gel (250 mL volume) with the aid of a small amount of pentane. The filtrate is concentrated in vacuo to afford the stannane **1** (6.95 g, 17.1 mmol, 57%) as a pale yellow oil. The quality of the crude product **1** is generally comparable to material prepared from the mesylate. However, in practice, we have preferred the use of the mesylate method, in spite of the additional steps required for preparation of the starting alcohol and its sulfonate. Hexabutylditin is the major impurity in these samples (approximately 15%). For the characterization of stannane **1**: R_f = 0.75 (SiO_2, 20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (1 H, d, *J* = 1.1 Hz), 5.00 (1 H, d, *J* = 1.1 Hz), 2.32 (2 H, br s), 1.60–1.44 (6 H, m), 1.37–1.25 (6 H, m), 0.98 (6 H, t, *J* = 8.0 Hz), 0.90 (6 H, t, *J* = 8.0 Hz) (Sn satellites are not reported). ^{13}C NMR (101 MHz, benzene-d_6): δ = 135.4, 111.2, 29.5, 27.8, 26.7, 14.0, 10.2.

Stock solutions of reagent **1** are prepared in dry CH_2Cl_2 or toluene, and aliquots of these solutions are directly utilized based upon the percent weight of **1**. Dichloromethane solutions of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene are stored in the freezer (–20 °C) under argon for one week without signs of deterioration. However, samples stored at 0 °C showed increasing intensity of a singlet in the ^{1}H NMR spectrum which indicates the formation of allene (δ = 4.68 ppm). Our preparation of stannane **1** provides a thermally labile product which undergoes an accelerating rate of decomposition upon standing at 22 °C overnight. The reagent **1** is generally unstable in the presence of aqueous acids and suffers decomposition on attempts for standard silica gel flash chromatography. The use of deactivated or basified silica gel fails to improve the overall purity of the sample. The presence of hexabutylditin does not adversely affect S_E' reactions of **1** with aldehydes as described in Scheme 1, eq.

1–4. However, we assume that stannylated impurities may suppress optimal yields of the radical-based reactions of Table 1.

In summary, a detailed experimental procedure reports the preparation of 2-bromo-3-(tri-*n*-butylstannyl)-1-propene, including spectroscopic characterization data. The instability of this reagent and major impurities have been described using HRMS and ^{1}H NMR sample analysis. This bifunctional reagent undergoes C–C bond-forming radical reactions with α-bromocarbonyl compounds and demonstrates excellent reactivity at –78 °C in S_E' processes with aldehydes. Stannane **1** should prove generally useful in a variety of mild transmetalation reactions.

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Supporting Information

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References and Notes

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(3) New address: N. Zorn, F. Hoffmann-La Roche AG, 4070 Basel, Switzerland.
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(17) The allylic alcohol 2-bromo-1-propen-3-ol (10.6 g, 64.3 mmol) was dissolved in CH_2Cl_2 at 0 °C, and Et_3N (10.3 mL, 73.9 mmol) was added under inert atmosphere. After stirring for 5 min, methanesulfonyl chloride (5.72 mL, 73.9 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to 22 °C with continued stirring over 2 h. TLC (20% EtOAc in hexanes) shows the production of a less polar mesylate and the disappearance of starting alcohol. The reaction mixture was concentrated under reduced pressure to approximately one-third of its volume, and the concentrate was diluted with Et_2O (150 mL). The mixture was filtered through a pad of Celite® to remove the triethylammonium hydrochloride precipitate with the aid of additional quantities of Et_2O. The filtrate was concentrated in vacuo to give the crude mesylate as a yellow oil with yields consistently in the 85–90% range. Vacuum distillation (1.4 mm Hg pressure) by Kugelrohr bulb-to-bulb transfer at an oven temperature of 60 °C afforded product as a colorless liquid which was judged to be >97% pure based on the ^{1}H NMR and ^{13}C NMR spectra of these samples. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (1 H), 5.78 (1 H), 4.81 (2 H), 3.09 (3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 124.1, 121.7, 72.3, 38.5). HRMS (CI): *m/z* calcd for $C_4H_8BrO_3S$ $[M + H]^+$ 214.9372; found: 214.9372. This mesylate was directly utilized in the next step.
(18) Darwish, A.; Chong, J. M. *Synth. Commun.* **2004**, *34*, 1885.