

Highly Stereo- and Regioselective Synthesis of (Z)-Trisubstituted Alkenes via 1-Bromo-1-alkyne Hydroboration–Migratory Insertion–Zn-Promoted Iodinolysis and Pd-Catalyzed Organozinc Cross-Coupling

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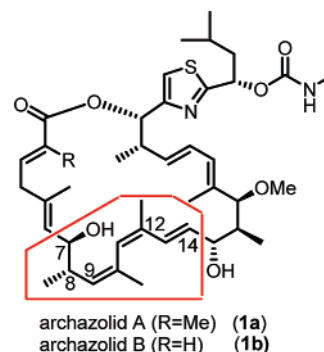
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Abstract: Hydroboration of 1-bromo-1-alkynes with dibromoborane followed by addition of 3 or 4 equiv of Me_2Zn provides an efficient and selective route to (Z)-2-alkenyldimethylboranes (**3**) or (Z)-2-alkenylmethylzincs (**4**), respectively, which have been successfully applied to one-pot Suzuki (B-I) or Negishi (Zn-I) coupling in some less demanding cases. However, in more demanding cross-coupling reactions, only the use of either (Z)-2-alkenyliodides (**5**) or the alkenylzincs prepared from lithiation and then zincation of **5** proves to be highly satisfactory (Zn-II or Zn-III protocol). On the contrary, the corresponding organoboron coupling under B-II or B-III protocol appears to be less satisfactory. Preliminary studies indicate that certain substituents proximal to trisubstituted alkenes seriously affect the course of the desired alkenylboron cross-coupling.

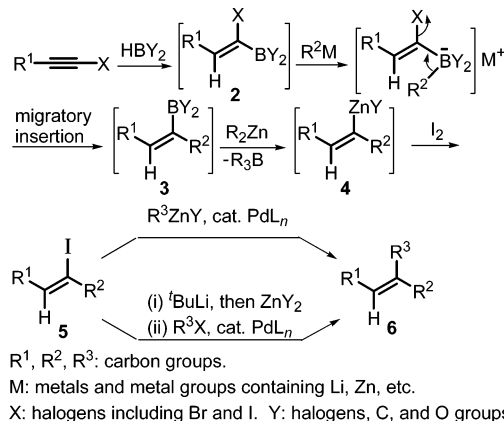
Introduction

Highly substituted conjugated dienes and oligoenes, especially those that contain tri- and tetrasubstituted Z alkenes, continue to provide major synthetic challenges. Archazolid A (**1a**) and B (**1b**) (Scheme 1), highly potent vacuolar-type ATPase inhibitors,^{1a} for example, possess a conjugated triene fragment, in which the C9–C12 conjugated diene component is a very rare example of (Z,Z)-1,1,3,4-tetrasubstituted 1,3-dienes with a proximal methyl-branching asymmetric carbon center in the C8 position. Even though an attractive and selective route to this class of conjugated dienes has just been devised^{1b} through the use of the Still–Gennari modification² of the Horner–Wadsworth–Emmons olefination,³ no widely applicable satisfactory alkenyl–alkenyl cross-coupling route has been available. We report herein an efficient and strictly stereoselective method for this and related classes of compounds requiring Pd-catalyzed alkenylation that is complementary with C=C bond-generating carbonyl olefination routes. It should be applicable to the synthesis of not only **1** but also other related synthetically demanding (Z)-trisubstituted alkenes and their derivatives. It consists of (i) 1-halo-1-alkyne hydroboration, (ii) migratory insertion of 1-halo-1-alkenylboron derivatives, (iii) Zn-promoted transmetalative iodinolysis, and (iv) Pd-catalyzed cross-coupling with alkenylzincs, requiring isolation of only **5** and the product (**6**) (Scheme 2).

Scheme 1



Scheme 2

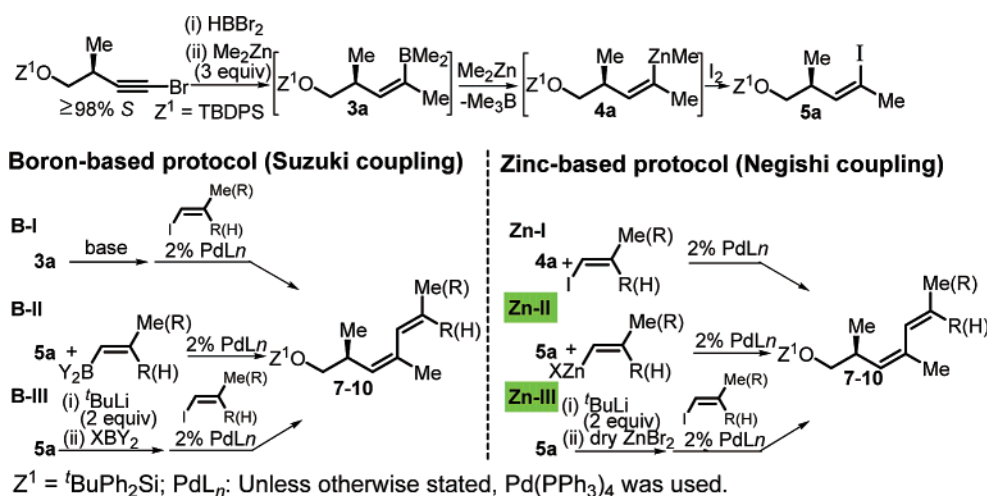


Results and Discussion

Highly regio- and stereoselective hydroboration of 1-halo-1-alkynes to give **2** in excellent yields, and their subsequent

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Scheme 3



Product	isolated product yield, %					
	direct use of 3a/ 4a		with isolated 5a			
	B-I ^a	Zn-I	B-II ^b	B-III ^b	Zn-II	Zn-III
 7a (Z²=H) 7b (Z²=TBS)	<5	<5	42 (7a)	40 (7b)	84 (7a)	78 (7b)
 8a (Z²=H) 8b (Z²=TBS)	c	c	28 (8a)	31 (8b)	83 (8a)	81 (8b)
 9	c	c	c	c	c	63
 10a (Z²=H) 10b (Z²=TBS)	<5	<5	c	48 (10b)	84 (10b)	80 (10a)

^a BY₂ in 3a is BMe₂. ^b Alkenyllithiums generated in situ were treated with *B*-MeO-9-BBN

c Not Performed.

migratory insertion to produce **3** with strict inversion of configuration, explored by Zweifel⁴ and exploited by us to devise the first highly selective and potentially general method for the synthesis of (*E,E*)-conjugated dienes in 1973,⁵ was one of the key developments of an alkenylboron-based general and stereoselective methodology for the synthesis of conjugated dienes and related compounds.⁶ Although trisubstituted alkene intermediates, such as **2** and **3**, were generated, the protonolysis of the C–B bonds led only to the formation of disubstituted alkenes and their derivatives. This method was soon supplanted by the Pd-catalyzed cross-coupling with Al,^{7,8} Zn,^{8,9} and Zr,^{8,10} discovered and developed by us ca. 1976–1978 and by subsequent developments involving orga-

nometals containing B,¹¹ Cu,¹² Sn,¹³ and others.¹⁴ Particularly noteworthy is the direct Pd-catalyzed cross-coupling of **3** to give **6** developed by Suzuki in 1986.¹⁵ Despite the efficiency and high stereoselectivity observed in some conjugated diene syntheses by this reaction, which have been experimentally reproduced (*vide infra*), our many attempts have failed to produce a model diene (**7**) via Pd-catalyzed Suzuki cross-coupling of **3a** and the corresponding iodide (**B-I** protocol) for the synthesis of **1**. Direct use of in situ generated alkenylzinc derivatives (**4**) (**Zn-I** protocol) has thus far been of limited success toward synthesis of **7** or **8** as well. In marked contrast,

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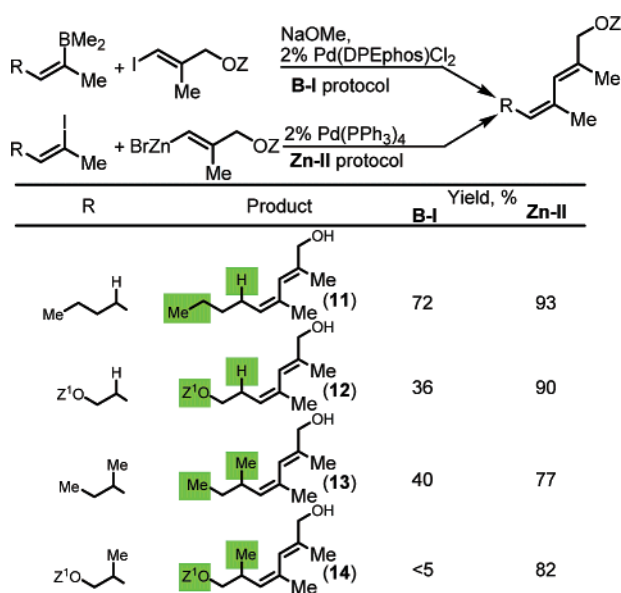
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Scheme 4



conversion and isolation of **3** into alkenyl iodide (**5**) via transmetalative iodinolysis, developed by Knochel,¹⁶ permit clean and high-yielding Pd-catalyzed cross-coupling with organozincs to produce **6** including **7** and a more advanced intermediate **8** (**Zn-II** protocol) well-suited for the synthesis of **1**. To the best of our knowledge, the method shown in Scheme 2 appears to be the only currently known convenient and highly ($\geq 98\%$) selective synthesis of (*Z,Z*)-dienes of the type represented by **7** and **8** via alkenyl–alkenyl coupling. Some comparative experimental results via different protocols (**Zn-I**, **Zn-II**, **Zn-III** and **B-I**, **B-II**, **B-III**) are summarized in Scheme 3.

In view of an earlier claim of the synthesis of **11** in 70% yield by the use of (*E*)-3-bromo-2-methyl-2-propen-1-ol and 3 mol % of Pd(PPh₃)₄ as a catalyst,¹⁵ its synthesis was carried out by the use of (*E*)-3-iodo-2-methyl-2-propen-1-ol, which led to a clean formation of **11** in 72% yield (Scheme 4). The striking difference between the results observed in the syntheses of **10** (Scheme 3) and **11** must be attributable to the presence of Me and TBDPSO groups in **10** and their absence in **11**, respectively. Indeed, the results shown in Scheme 4 indicate that the presence of either group in the indicated positions is detrimental to the organoborane protocol,¹⁵ but that the **Zn-II** protocol is not noticeably affected by their presence.

Although the major attention of this work has been focused on the development of efficient and selective procedures applicable to the synthesis of archazolid A and B, the protocol represented by Scheme 2 is widely applicable to the synthesis of a variety of (*Z*)-trisubstituted alkenes. In view of the wide occurrence of natural products derivable via **5a** containing either an alkene-bound Me or Et group, **15–22** have been prepared in uniformly high yields (70–95%) and selectivity ($\geq 97–98\%$) as summarized in Scheme 5. In some cases, e.g., synthesis of **15–18**, the **Zn-I** protocol is very satisfactory, but the **Zn-II** protocol using isolated alkenyl iodides is more widely applicable and dependable, as demonstrated by the

synthesis of **15**, **16**, and **19–21**. It should be noted that **19** would serve as a potentially attractive intermediate for the synthesis of discodermolide (**23**).¹⁷ Alternatively, carbonyl-containing reagents may preferably be introduced as the electrophilic cross-coupling partner. In such cases, the **Zn-III** protocol, which has been shown to be far superior to the **Zn-I** protocol, should provide the best option, as exemplified by the synthesis of **22**. Application of **22** to the synthesis of callistatin A (**24**)¹⁸ appears eminently feasible, and such efforts are in progress.

Any other convenient and selective routes to **5** would provide synthetic equivalents to that shown in Scheme 2, although none of the previously developed protocols appear to have been applied to the synthesis of (*Z,Z*)-1,1,3,4-tetrasubstituted 1,3-dienes. One notable example is the four-step conversion of 1-alkynes into **5** via silylation–hydrozirconation followed by iodinolysis–cross-coupling–desilylative iodinolysis,¹⁹ which suffers from the need for isolation of three intermediates. Conversion of aldehydes to 1,1-dibromo-1-alkenes followed by stepwise cross-coupling with inversion in the second step developed recently by us,²⁰ in principle, is a more efficient route to **6**. However, both the Pd-catalyzed trans-selective monosubstitution and the Pd-catalyzed second substitution with inversion in more demanding cases appear to require further development.

Conclusions

(1) Hydroboration of 1-bromo-1-alkynes with dibromoborane⁴ followed by addition of 3 equiv of Me₂Zn provides (*Z*)-2-alkenyldimethylboranes (**3**), whereas the use of 4 equiv of Me₂Zn leads to the formation of the corresponding (*Z*)-2-alkenylmethylzincs (**4**).⁴ The use of Et₂Zn in place of Me₂Zn provides the corresponding Et-substituted compounds.

(2) Although iodinolysis of **3** with I₂ has not been satisfactory in our hands, that of **4** with I₂ readily affords the corresponding iodides **5** in high yields. The (*Z*)-2-alkenyl iodides thus obtained can be converted to the bromozinc derivatives or the borane derivatives via lithiation with 2 equiv of ^tBuLi, followed by treatment with dry ZnBr₂ or appropriate boranes, respectively.

(3) In less demanding cases, the cross-coupling of either alkenylboranes (**3**) or alkenylzincs (**4**) catalyzed by Pd(PPh₃)₄ or Pd(DPEphos)Cl₂ can proceed satisfactorily (See the results obtained by the use of **B-I** protocol and **Zn-I** protocol in Schemes 4 and 5).

(4) In more demanding cases, such as those shown in Schemes 3 and 4, however, neither **B-I** nor **Zn-I** protocol proved satisfactory, the yields of the desired products being $\leq 40\%$. In such cases, the use of either isolated alkenyl iodides (**Zn-II** protocol) or the alkenylzincs derived from the isolated iodides

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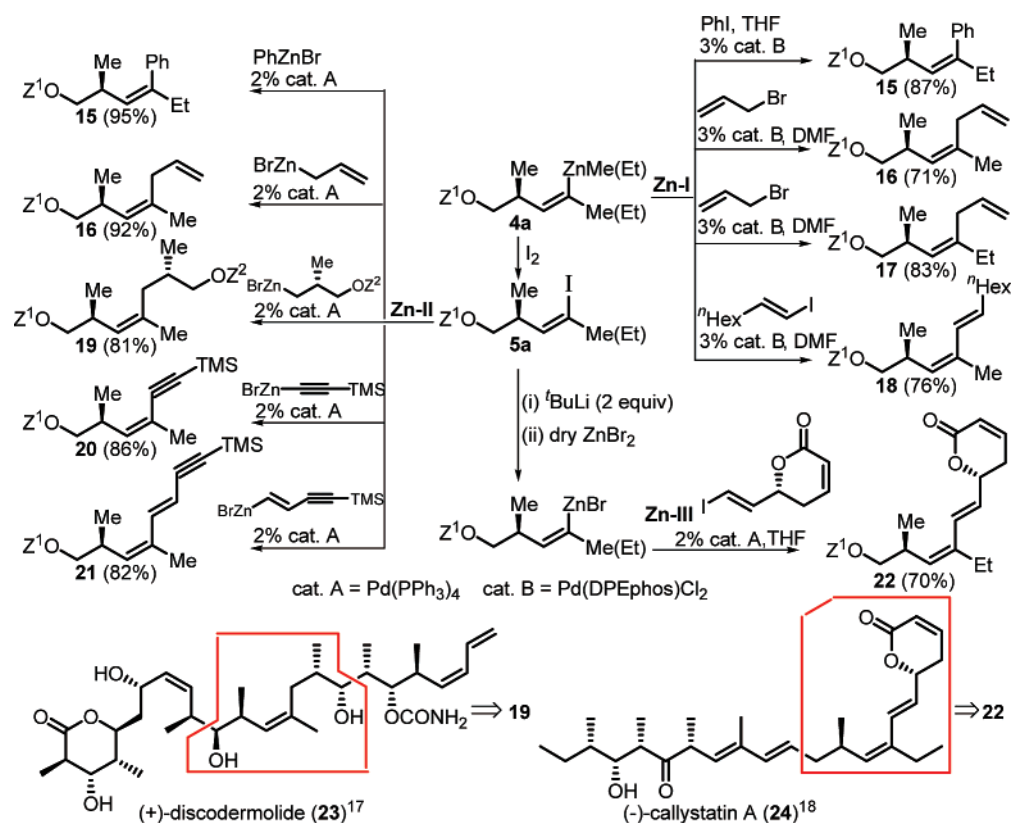
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Scheme 5



(Zn-III protocol) in the Negishi coupling proved to be highly satisfactory (Schemes 2–4). On the contrary, the corresponding organoboron cross-coupling under the B-II or B-III protocol has thus far been disappointing (Scheme 3).

(5) There are clear indications that certain substituents proximal to the crucial trisubstituted alkenes, such as branching Me and alkyl groups in the allylic position and β -silyloxy groups seriously affect the course of the desired Pd-catalyzed alkenylation (Scheme 4). Fortunately, the Zn-II and/or Zn-III protocols have provided satisfactory procedures for all of the demanding cases that have thus far been tested. Both Zn-II and Zn-III protocols have provided potential intermediates **8a** and **8b**, respectively, for the synthesis of archazolides A and B (**1a** and **1b**) in 83 and 81% yields, respectively, as isomerically $\geq 98\%$ pure compounds.

Experimental Section

Several representative procedures are listed below. The experimental procedures and spectroscopic data for all compounds can be found in the Supporting Information.

(4Z,6S)-7-(tert-Butyldiphenylsilyloxy)-4,6-dimethyl-1,4-heptadiene (16): Representative Procedure for the Use of In Situ Generated (Z)-4-Methyl-2-alkenylzincs (Zn-I Protocol). To a solution of (3S)-4-(tert-butyldiphenylsilyloxy)-3-methyl-1-bromo-1-butyne (0.21 g, 0.50 mmol) in toluene (0.50 mL) in a Schlenk flask capped with a rubber septum, was added Br₂BH (0.50 mL, 1.0 M in CH₂Cl₂, 0.50 mmol) at 23 °C, and then the reaction mixture was warmed to 70 °C and kept at this temperature for 1 h. The resultant mixture was cooled to –78 °C, and Me₂Zn (1.0 mL, 2.0 M in toluene, 2.0 mmol) was added dropwise. After 10 min at –78 °C, the reaction mixture was warmed to 0 °C. After 20 min, the rubber septum was replaced with a glass stopper under a steady flow of Argon, and most of the volatiles were removed in vacuo. The resulting organozinc reagent was redissolved in THF

(2.0 mL) at 0 °C, treated with allyl bromide (0.12 g, 1.0 mmol) and Pd(DPEphos)Cl₂ (7.2 mg, 10 μ mol) in DMF (3.0 mL), warmed to 23 °C, and monitored by GLC analysis. The reaction was complete in 6 h, and the reaction mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes–EtOAc) afforded 0.13 g (71%) of the desired product **16**: ¹H NMR (300 MHz, CDCl₃) δ 1.01 (d, *J* = 6.6 Hz, 3H), 1.13 (s, 9H), 1.78 (s, 3H), 2.45–2.85 (m, 3H), 3.45–3.7 (m, 2H), 4.95–5.2 (m, 3H), 5.7–5.85 (m, 1H), 7.4–7.55 (m, 6H), 7.7–7.85 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 13.59, 18.77, 20.28, 27.86 (3C), 36.11, 36.26, 69.83, 115.87, 128.42, 128.56 (4C), 130.47 (2C), 135.05 (2C), 136.65 (4C), 137.83, 139.76. HRMS calcd. for C₂₅H₃₄OSi, 378.2379; found, 378.2377.

(2Z,4Z,6S)-7-(tert-Butyldiphenylsilyloxy)-2,4,6-trimethyl-2,4-heptadien-1-ol (7a): Representative Procedure for the Use of Isolated (Z)-4-Methyl-2-alkenyl Iodides for the Negishi Coupling (Zn-II Protocol). A solution of (1Z)-3-(tert-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.32 g, 1.0 mmol) in ether (2.0 mL) was treated with ^tBuLi (1.2 mL, 1.7 M in pentane, 2.0 mmol) at –78 °C for 30 min and then with a solution of dry ZnBr₂ (0.23 g, 1.0 mmol) in THF (1.5 mL) at –78 °C for 10 min. The reaction mixture was warmed to 0 °C over 30 min, treated with a solution of **5a** (0.37 g, 0.80 mmol) and Pd(PPh₃)₄ (23 mg, 0.020 mmol) in THF (1.5 mL), warmed to 23 °C, and monitored by GLC analysis. The reaction was complete in 5 h, and the reaction mixture was quenched with aqueous NH₄Cl, extracted with ether, washed successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated to give a viscous oil. To this crude product in THF (3.5 mL) were added 6 drops of 1 N HCl at 23 °C, and the resultant mixture was monitored by TLC analysis. After the complete removal of the TBS group (~30 min), the mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes–EtOAc) afforded

0.27 g (84% over 2 steps) of the desired product **7a**: ^1H NMR (300 MHz, CDCl_3) δ 0.99 (d, $J = 6.6$ Hz, 3H), 1.13 (s, 9H), 1.35 (br, 1H), 1.82 (s, 3H), 1.92 (d, $J = 1.8$ Hz, 3H), 2.55–2.65 (m, 1H), 3.52 (d, $J = 6.3$ Hz, 2H), 4.05–4.25 (m, 2H), 5.12 (d, $J = 9.9$ Hz, 1H), 5.79 (s, 1H), 7.4–7.55 (m, 6H), 7.7–7.8 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.13, 19.35, 20.84, 24.65, 26.93 (3C), 36.22, 62.95, 68.79, 127.07, 127.66 (4C), 129.62 (2C), 131.45, 132.88 (2C), 133.94 (2C), 135.74 (4C). HRMS calcd. for $\text{C}_{26}\text{H}_{36}\text{O}_2\text{Si}$, 408.2485; found, 408.2483.

(2Z,4Z,6S)-1-(tert-Butyldimethylsilyloxy)-7-(tert-butylidiphenylsilyloxy)-2,4,6-trimethyl-2,4-heptadiene (7b): Representative Procedure for the Use of (Z)-4-Methyl-2-alkenylzincs Generated from the Corresponding Alkenyl Iodides (Zn-III Protocol). A solution of **5a** (0.46 g, 1.0 mmol) in ether (2.0 mL) was treated with $^t\text{BuLi}$ (1.2 mL, 1.7 M in pentane, 2.0 mmol) at -78°C over 30 min and then with a solution of dry ZnBr_2 (0.23 g, 1.0 mmol) in THF (1.5 mL) at -78°C for 10 min. The reaction mixture was warmed to 0°C over 30 min, treated with $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) and (1Z)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.25 g, 0.80 mmol) in THF (1.5 mL), warmed to 23°C , and monitored by GLC analysis. The reaction was complete in 4 h, and the reaction mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated. Flash chromatography (silica gel, 98/2 hexanes-EtOAc) afforded 0.33 g (78%) of the desired product **7b**: ^1H NMR (300 MHz, CDCl_3) δ 0.11 (s, 6H), 0.97 (s, 9H), 1.04 (d, $J = 6.4$ Hz, 3H), 1.13 (s, 9H), 1.81 (s, 3H), 1.88 (d, $J = 1.2$ Hz, 3H), 2.4–2.6 (m, 1H), 3.4–3.6 (m, 2H), 4.12 (s, 2H), 5.11 (d, $J = 10.2$ Hz, 1H), 5.72 (s, 1H), 7.4–7.55 (m, 6H), 7.7–7.8 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ -5.24 (2C), 17.08, 18.42, 19.38, 20.67, 24.49, 26.0 (3C), 26.93 (3C), 36.14, 62.89, 68.53, 125.72, 127.6 (4C), 129.54 (2C), 131.11, 132.68, 134.14 (2C), 135.71 (4C), 136.19.

(2E,4Z)-2,4-Dimethyl-2,4-nonadien-1-ol (11): Representative Procedure for the Use of in Situ Generated (Z)-2-Alkenylborons (B-I Protocol). To a solution of 1-bromo-1-hexyne (80 mg, 0.50 mmol) in toluene (0.50 mL) was added Br_2BH (0.50 mL, 1.0 M in CH_2Cl_2 , 0.50 mmol) at 23°C , and then the reaction mixture was warmed to 70°C and kept at this temperature for 1 h. The resultant mixture was cooled to -78°C , and Me_2Zn (0.75 mL, 2.0 M in toluene, 1.5 mmol) was added dropwise. After 10 min at -78°C , the reaction mixture was warmed to 0°C over 30 min, treated with a solution of (1E)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.13 g, 0.42 mmol), $\text{Pd}(\text{DPEphos})\text{Cl}_2$ (7.2 mg, 10 μmol), and NaOMe (1.0 mL, 1.0 M in MeOH, 1.0 mmol) in DMF (3.0 mL), warmed to 60°C , and monitored by GLC analysis. The reaction was complete in 10 h, and the reaction mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes-EtOAc) afforded 51 mg (72%) of the desired product **11**: ^1H NMR (300 MHz, CDCl_3) δ 0.75–0.95 (m, 3H), 1.2–1.35 (m, 4H),

1.5 (t, $J = 6.0$ Hz, 1H), 1.65 (d, $J = 0.9$ Hz, 3H), 1.76 (s, 3H), 1.85–1.95 (m, 2H), 4.07 (d, $J = 5.4$ Hz, 2H), 5.25 (t, $J = 7.5$ Hz, 1H), 5.89 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.1, 15.28, 22.49, 23.9, 28.87, 31.84, 68.79, 124.93, 128.72, 131.84, 136.16. HRMS calcd. for $\text{C}_{11}\text{H}_{20}\text{O}$ 168.1514, found 168.1512.

7a: Representative Procedure for the Use of Isolated (Z)-4-Methyl-2-alkenyl Iodides (B-II Protocol). A solution of (1Z)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.32 g, 1.0 mmol) in ether (2.0 mL) was treated with $^t\text{BuLi}$ (1.2 mL, 1.7 M in pentane, 2.0 mmol) at -78°C over 30 min, and *B*-methoxy-9-BBN (1.0 mL, 1.0 M in hexanes, 1.0 mmol) at -78°C for 10 min. The reaction mixture was warmed to 0°C over 30 min, treated with a solution of **5a** (0.37 g, 0.80 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), and $\text{Pd}(\text{DPEphos})\text{Cl}_2$ (14 mg, 0.020 mmol) in DMF (1.5 mL), warmed to 60°C , and monitored by TLC analysis. The reaction was complete in 14 h, and the reaction mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated to give a viscous oil. To this crude product in THF (3.5 mL) was added 3 drops of 1 N HCl at 23°C , and the resultant mixture was monitored by TLC analysis. After the complete removal of the TBS group (~ 30 min), the mixture was quenched with aqueous NH_4Cl , extracted with ether, washed successively with saturated NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes-EtOAc) afforded 0.14 g (42% over 2 steps) of the desired product **7a**.

7b: Representative Procedure for the Use of (Z)-4-Methyl-2-alkenylborons Generated from the Corresponding Alkenyl Iodides (B-III Protocol). A solution of **5a** (0.46 g, 1.0 mmol) in ether (2.0 mL) was treated with $^t\text{BuLi}$ (1.2 mL, 1.7 M in pentane, 2.0 mmol) at -78°C over 30 min, and then with *B*-methoxy-9-BBN (1.0 mL, 1.0 M in hexanes, 1.0 mmol) at -78°C for 10 min. The reaction mixture was warmed to 0°C over 30 min, treated with a solution of (1Z)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.25 g, 0.80 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol) and $\text{Pd}(\text{DPEphos})\text{Cl}_2$ (14 mg, 0.020 mmol) in DMF (1.5 mL), warmed to 60°C , and monitored by TLC analysis. The reaction was complete in 16 h, and the reaction mixture was quenched with 1 N HCl, extracted with ether, washed successively with saturated NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated. Flash chromatography (silica gel, 98/2 hexanes-EtOAc) afforded 0.17 g (40%) of the desired product **7b**.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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