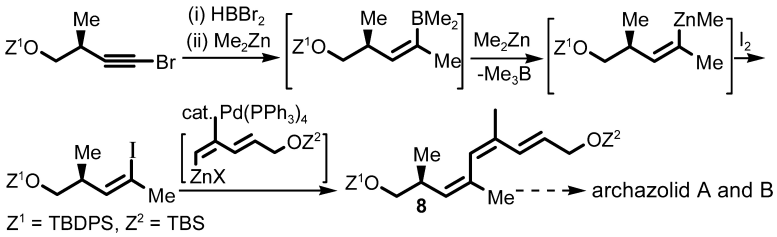
Article

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

Zhihong Huang, and Ei-ichi Negishi

J. Am. Chem. Soc., **2007**, 129 (47), 14788-14792 • DOI: 10.1021/ja0772039



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 11/07/2007

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

Zhihong Huang and Ei-ichi Negishi*

Contribution from the Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

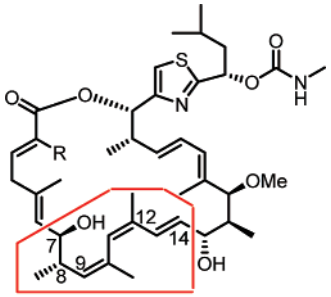
Received September 17, 2007; E-mail: negishi@purdue.edu

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.

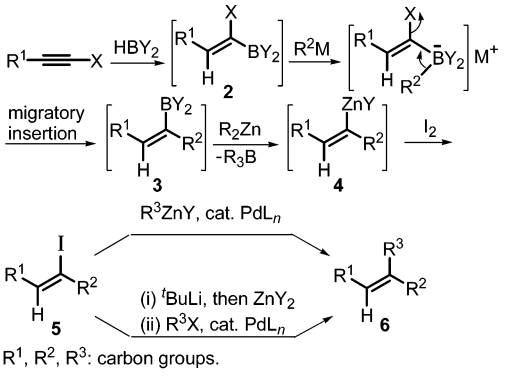
Introduction

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 modification[2] 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



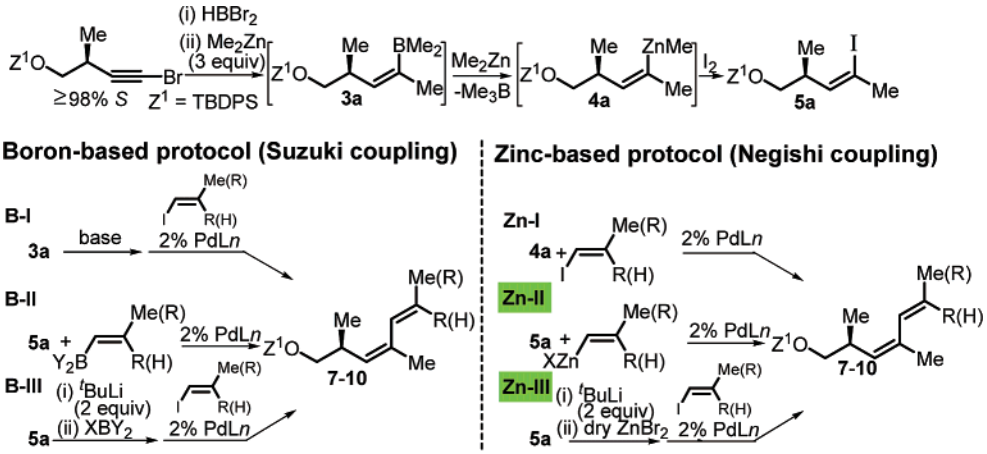
Results and Discussion

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

(1) (a) Hassfeld, J.; Farès, C.; Steinmetz, H.; Carlomagno, T.; Menche, D. *Org. Lett.* **2006**, *8*, 4751. (b) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100.
(2) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(3) (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

10.1021/ja0772039 CCC: $37.00

Scheme 3



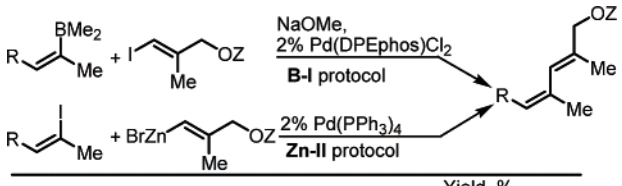
Product	isolated product yield, % direct use of 3a/ 4a B-I[a]	Zn-I	with isolated 5a B-II[b]	B-III[b]	Zn-II	Zn-III
7a (Z^2=H) **7b** (Z^2=TBS)	<5	<5	42 (**7a**)	40 (**7b**)	84 (**7a**)	78 (**7b**)
8a (Z^2=H) **8b** (Z^2=TBS)	*c*	*c*	28 (**8a**)	31 (**8b**)	83 (**8a**)	81 (**8b**)
9	*c*	*c*	*c*	*c*	*c*	63
10a (Z^2=H) **10b** (Z^2=TBS)	<5	<5	*c*	48 (**10b**)	84 (**10b**)	80 (**10a**)

[a] BY_2 in **3a** is BMe_2. [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 Zweifel[4] 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 organometals 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,

(4) (a) Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086. (b) Chen, Y. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3702.
(5) (a) Negishi, E.; Yoshida, T. *J. Chem. Soc. Chem. Commun.* **1973**, 606. (b) For its application to the synthesis of (*E*)-1,4-disubstituted 1,2,3-butatrienes, see: Yoshida, T.; Williams, R. M.; Negishi, E. *J. Am. Chem. Soc.* **1974**, *96*, 3688.
(6) For the synthesis of (*E*,*Z*)-1,4-disubstituted conjugated dienes, see: (a) Negishi, E.; Lew, G.; Yoshida, T. *J. Chem. Soc. Chem. Commun.* **1973**, 874. (b) Negishi, E.; Abramovitch, A. *Tetrahedron Lett.* **1977**, 411.
(7) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
(8) (a) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N.; Luo, F. T. *J. Am. Chem. Soc.* **1987**, *109*, 2393.
(9) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc. Chem. Commun.* **1977**, 683.
(10) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027.
(11) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(12) (a) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959. (b) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 1589.
(13) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (b) For a review, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(14) For reviews containing discussions of Pd-, Ni-catalyzed cross-coupling with other metals, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*, 2 Vols.; Wiley-Interscience: New York, 2002, Part III, pp 215−1119. (b) de Meijere, A.; Diedcrich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2 Vols.; Wiley-VCH: Weinheim, 2004, p 916.
(15) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.

Scheme 4



R	Product	Yield, % B-I	Zn-II
Me	(11)	72	93
Z¹O	(12)	36	90
Me	(13)	40	77
Z¹O	(14)	<5	82

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 (≥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 $Pd(PPh_3)_4$ 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 (≥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 callystatin 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 dibromoborane[4] followed by addition of 3 equiv of Me_2Zn provides (*Z*)-2-alkenyldimethylboranes (**3**), whereas the use of 4 equiv of Me_2Zn leads to the formation of the corresponding (*Z*)-2-alkenylmethylzincs (**4**).[4] The use of Et_2Zn in place of Me_2Zn provides the corresponding Et-substituted compounds.

(2) Although iodinolysis of **3** with I_2 has not been satisfactory in our hands, that of **4** with I_2 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 ^{t}BuLi, followed by treatment with dry $ZnBr_2$ or appropriate boranes, respectively.

(3) In less demanding cases, the cross-coupling of either alkenylboranes (**3**) or alkenylzincs (**4**) catalyzed by $Pd(PPh_3)_4$ or $Pd(DPEphos)Cl_2$ 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 ≤40%. In such cases, the use of either isolated alkenyl iodides (**Zn-II** protocol) or the alkenylzincs derived from the isolated iodides

(16) (a) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P. Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229. (b) Oppolzer, W.; Radinov, R.; Brabander, J. D. *Tetrahedron Lett.* **1995**, *36*, 2607.

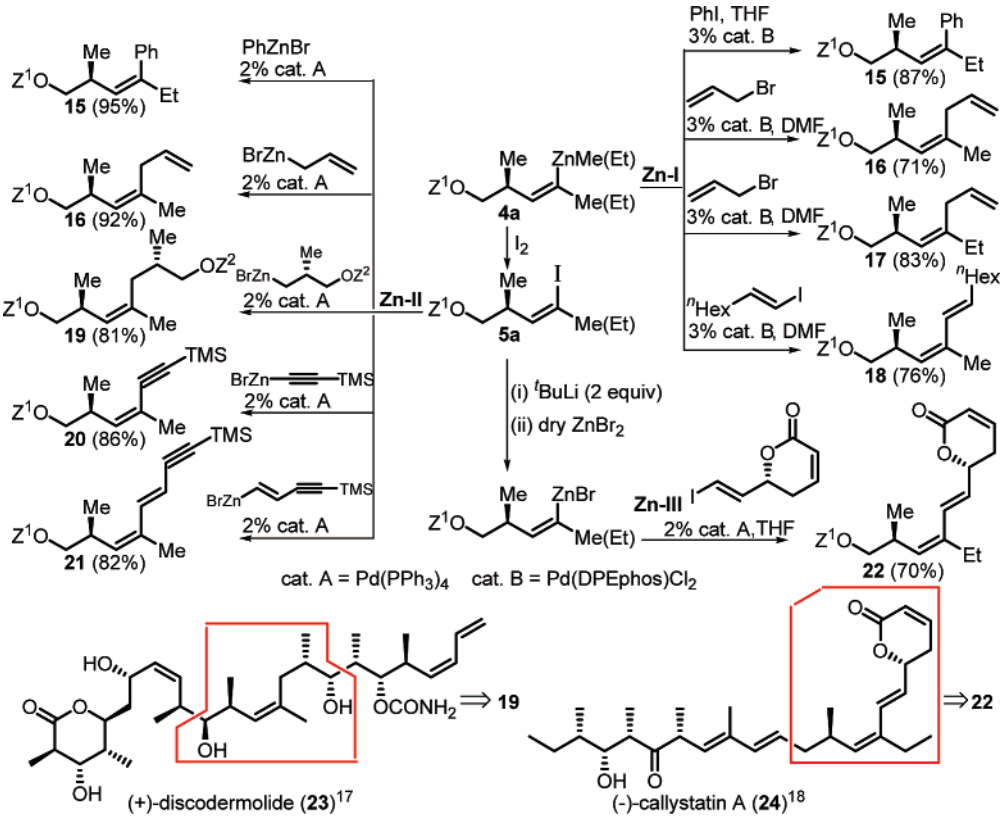
(17) (a) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (b) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098. (c) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (d) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 377.

(18) (a) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349. (b) Smith, A. B., III.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (c) Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107. (d) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751. (e) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993. (f) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203.

(19) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281.

(20) (a) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636. (b) Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 2259.

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 ≥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.

(4*Z*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimeth-yl-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 (3*S*)-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 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 (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 $Pd(DPEphos)Cl_2$ (7.2 mg, 10 μmol) 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 $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes-EtOAc) afforded 0.13 g (71%) of the desired product **16**: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{25}H_{34}OSi$, 378.2379; found, 378.2377.

(2*Z*,4*Z*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-2,4,6-tri-methyl-2,4-heptadien-1-o l (7a): Representative Procedure for the Use of Isolated (*Z*)-4-Methyl-2-alkenyl Iodides for the Negishi Coupling (Zn-II Protocol). A solution of (1*Z*)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.32 g, 1.0 mmol) in ether (2.0 mL) was treated with ^{t}BuLi (1.2 mL, 1.7 M in pentane, 2.0 mmol) at −78 °C for 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 a solution of 5a (0.37 g, 0.80 mmol) and $Pd(PPh_3)_4$ (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 NH_4Cl, 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) 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 $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, 95/5 hexanes-EtOAc) afforded

0.27 g (84% over 2 steps) of the desired product **7a**: ^{1}H 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 $C_{26}H_{36}O_2Si$, 408.2485; found, 408.2483.

(2*Z*,4*Z*,6*S*)-1-(*tert*-Butyldimethylsilyloxy)-7-(*tert*- butyldiphenylsilyloxy)-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}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 $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) and (1*Z*)-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**: ^{1}H 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.

(2*E*,4*Z*)-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 (1*E*)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.13 g, 0.42 mmol), $Pd(DPEphos)Cl_2$ (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**: ^{1}H 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 $C_{11}H_{20}O$ 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 (1*Z*)-3-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-propene (0.32 g, 1.0 mmol) in ether (2.0 mL) was treated with ^{t}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 $Pd(DPEphos)Cl_2$ (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}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 (1*Z*)-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 $Pd(DPEphos)Cl_2$ (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**.

Acknowledgment. We thank the National Science Foundation (CHE-0309613), the National Institutes of Health (GM 36792), and Purdue University for support of this work.

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.

JA0772039