Synthesis of 1,4-Dienes through the Regioselective Coupling of ((*E*)-1-Alkenyl)ethylzinc Reagents with Allylic Halides. The Effect of Catalyst and Solvent on the Outcome of This Reaction

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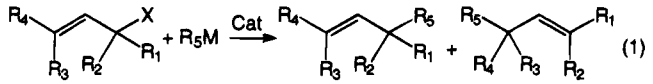
Received November 15, 1993

The cross-coupling of organometallics with organic halides is an important method of stereo- and regiospecific carbon–carbon bond formation. The vast majority of these reactions are either catalyzed or promoted by transition-metal compounds.[1] Various organic halides have been utilized as electrophilic partners in this reaction, among them, allylic halides. The most fundamental and important problem in the coupling of allylic compounds with organometallic reagents is regio- and stereocontrol, as shown by the following general equation (eq 1).[2]

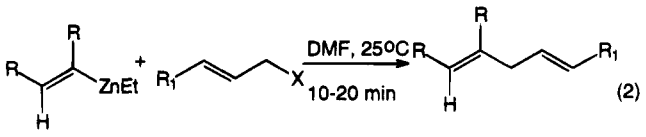


(1)

In this note, we report the direct and highly regioselective cross-coupling of stereochemically pure ((*E*)-1-alkenyl)ethylzincs with various allylic bromides, which results in the formation of stereodefined 1,4-dienes (eq 2).[3] The synthesis of the 1,4-diene structure has received great attention for several reasons. For instance, 1,4-dienes are common in naturally occurring fatty acids such as arachidonic acid, the biological precursor to the prostaglandins, and other polyunsaturated fatty acids.[4]

Total synthesis of polyunsaturated fatty acids with *cis* double bonds (having the 1,4-diene structure) is frequently accomplished by synthesis of the corresponding polyacetylenic compounds, followed by partial catalytic hydrogenation.[5] However, methylene-interrupted polyene compounds having *trans* and *cis* double bonds such as insect pheromones cannot be constructed in this way.[6] The discovery of transition metal catalyzed cross-coupling reactions of vinylic organometallics, obtained by hydrometalation or carbonmetalation of the corresponding alkynes,[7] with allylic substrates was a successful solution to that challenging problem.[8] Among them, those containing Al,[9] Zr,[10] Sn,[11] and Si[12] are the most utilized. In addition, 1-alkenylboranes, readily obtainable from alkynes via hydroboration, have been investigated thoroughly.[13] For instance, 1-alkenyldisiamylboranes undergo coupling with allylic bromides (100% excess is required) in refluxing benzene and in the presence of sodium hydroxide and catalytic amounts of $Pd(PPh_3)_4$ (3 mol %) to yield the corresponding 1,4-dienes in average to good yields, the Suzuki reaction.[13a,b]

We would like to emphasize the fact that all cross-coupling reactions described above require either stoichiometric or catalytic quantities of palladium or copper salts or complexes (analogous nickel species have been utilized in very few occasions). The type (S_N2 vs S_N2' allylic substitution) of regioselectivity exhibited in different reactions appears to depend mainly on the nature of both the organometallic partner and the allylic substrate.[9–13] However, added ligands such as maleic anhydride have been proven to control the coupling regiochemistry,[14] while in other cases the regiochemistry varies with the solvent used.[9] Furthermore, all the reactions proceed with retention of the stereochemistry of the double bond in the organometallic partner, even though stereochemical scrambling of the double bond of the allylic substrate has been observed in certain cases.[9,12,13e] More specifically, although pure (*E*)-crotyl acetate was used in the reaction mentioned above, both (2*E*,5*E*)- and (2*Z*,5*E*)-6-methyldodecadiene were formed (the *E*,*E* isomer was favored).[9]



(2)

1a,b (X=Br,I) **2**

1a: R=Et
1b: R=n-Pr

In the past, stereodefined alkenylzincs (RZnX) have usually been obtained by a multistep methodology involving an iodine–zinc exchange reaction.[15] We have recently shown that stereochemically pure (*E*)-alkenylzincs can be obtained readily from the corresponding (*Z*)-trialkenylboranes through transmetalation with dialkylzincs, in particular diethylzinc.[16] Depending on the boron-to-zinc ratio, either ((*E*)-1-alkenyl)ethylzinc or di-(*E*)-1-alkenylzinc is the predominant zinc species. There-

(1) (a) Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980; Chapter 11. (b) Noyori, R. *Transition Metal Organometallics in Organic Synthesis*; Alper, H., Ed.; Academic: New York, 1976; Vol. 1, p 93.

(2) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(3) This work was presented in part at the 205th American Chemical Society National Meeting, Denver, CO, March 28–April 2, 1993.

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(5) Axen, U.; Pike, E.; Schneider, W. P. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 1, p 81.

(6) Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845.

(7) For representative references see: (a) Hydroalumination: Wrackmeyer, B. In *Inorganic Reactions and Methods*; Zuckerman, J. J.; Hagen, A. P., Eds.; VCH: Deerfield Beach, 1989; Vol. 10, Chapter 5.3; p 141. (b) Carbometalation: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(8) For a useful review see: Trost, B. M. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 3, p 467.

(9) Negishi, E.; Chatterjee, S.; Matsushita, H. *Tetrahedron Lett.* **1981**, *22*, 3737.

(10) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882.

(11) (a) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (b) Stille, J. K.; Sheffy, F. K.; Godschalx, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4833.

(12) (a) Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161. (b) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

(13) For examples of coupling of 1-alkenylboranes with allylic derivatives see: (a) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865. (b) Miyaura, N.; Yano, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1471. (c) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761. (d) Hoshi, M.; Masuda, Y.; Nunokawa, Y.; Arase, A. *Chem. Lett.* **1984**, 1029. (e) Yatagai, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1670. (f) Yatagai, H. *J. Org. Chem.* **1980**, *45*, 1640. (g) Hoshi, M.; Masuda, Y.; Arase, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2855. (h) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 550.

(14) Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310.

(15) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

(16) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449.

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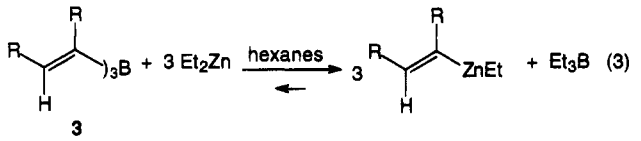
fore, in a 1:3 stoichiometry of boron-to-zinc, ((*E*)-1-alkenyl)ethylzinc is preferentially formed (eq 3).[17] We subsequently demonstrated that these reagents react *in situ* with aldehydes[16] and aryl iodides[18] to yield secondary allylic alcohols and stereodefined trisubstituted alkenes, respectively, in fair to very good yields under mild conditions, where alkenylboranes do not react.



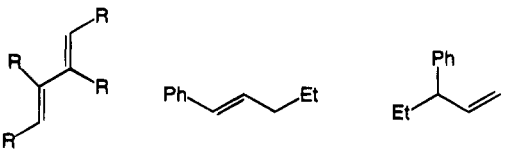
Results and Discussion

We have examined the reaction of ((*E*)-1-alkenyl)-ethylzincs with a series of allylic halides. To our surprise, we found that **1a** undergoes direct (no transition metal catalyst is required) cross-coupling with an unsubstituted allylic halide such as allyl bromide (1 equiv) to form (1,4*E*)-4-ethylheptadiene almost quantitatively. The choice of solvent appears to be vital for the success of this reaction. In hexanes, where transfer of the alkenyl groups from boron to zinc was shown to occur rapidly,[16] only traces of the cross-coupling product were detected (GC). The major product detected (GC) was the 1,3-diene compound **4a** (homocoupling product), derived from dimerization of the alkenylzinc species. The use of polar aprotic coordinating solvents such as DMF favors considerably the 1,4-diene formation, suppressing at the same time the homocoupling product. GC analysis of the product revealed that the geometry of the double bond on the organometallic species was retained throughout the whole reaction sequence. Allyl iodide was found to be equally effective as allyl bromide. On the other hand, allyl chloride was not as suitable as the previous two halides. In addition to the cross-coupling product, a substantial amount of the homocoupling product **4b** was formed. Surprisingly, allyl acetate failed to undergo an analogous reaction. The homocoupling product **4a** along with several other unidentified products were formed in this case.

Subsequently, we investigated the scope and limitations of this reaction (eq 2). Interesting results were obtained when a γ-monosubstituted allylic bromide such as crotyl bromide was utilized in a cross-coupling reaction with **1b**. The commercially available allylic compound is a mixture of geometrical and regional isomers. ^{1}H NMR analysis of the distilled sample indicated that the ratio of the two geometrical isomers was 5:1 in favor of the *E* isomer, while the ratio of 1-bromo-2-butenes over 3-bromo-1-butene was 6:1 in favor of the internal alkene. A pure analytical sample of the cross-coupling Product (mixture of (2*E*,5*E*)- and (2*Z*,5*E*)-5-propylnonadiene, and (1,4*E*)-3-methyl-4-propyloctadiene) was obtained by preparative TLC (silica gel, hexanes). ^{1}H NMR analysis of this sample revealed that the ratio of the two regioisomeric 1,4-dienes formed, (2*E*,5*E*)- and (2*Z*,5*E*)-5-propylnonadiene vs (1,4*E*)-3-methyl-4-propyloctadiene was approximately 5:1, and that the ratio of the two geometrical isomers, (2*E*,5*E*)- vs (2*Z*,5*E*)-5-propylnonadiene was 6:1. These results indicate clearly that the reaction proceeded with a high degree of regioselectivity for the less highly substituted carbon in the allylic skeleton. Moreover, it is equally significant that the double bond geometry of the allylic partner was also retained. GC analysis of the same sample was in full agreement with these conclusions.

Cinnamyl bromide coupled directly with **1b** under this set of conditions. This reaction furnished (1*E*,4*E*)-1-phenyl-4-propyloctadiene, the S_N2 substitution product, in good yield. However, the other regioisomer, (1,4*E*)-3-phenyl-4-propyloctadiene, as well as the regioisomeric cross-coupling products **5** and **6** derived from competitive ethyl transfer, was also formed in very small amounts. Unfortunately, we were unable to separate these minor side products from the major S_N2 substitution product by column chromatography.

Methyl 4-bromocrotonate could also react with **1b** under our standard conditions, even though the regioselectivity for the α-substituted product was not so high. In particular, (2*E*,5*E*)-5-propylnonadienoic acid methyl ester was formed, along with (3*E*)-2-ethenyl-3-propylheptenoic acid methyl ester, in a 72:28 ratio, according to GC analysis of the crude product. The overall yield of the cross-coupling product was lower than previous examples.



4a,b **5** **6**

4a: R=Et
4b: R=n-Pr

The reaction of **1a** with 4-bromocrotononitrile (mixture of geometrical isomers, *Z*/*E*, 55:45) also proceeded with retention of the double geometry of the allylic partner (within experimental error). GC analysis, along with the ^{1}H NMR spectrum of the crude coupling product showed that (2*Z*,5*E*)- and (2*E*,5*E*)-5-ethyloctadienonitrile were formed in equal amounts (50:50). It is noteworthy that the α-attack product was formed exclusively, even though the isolated yield was pretty low.

Summarizing our results thus far, we have shown that representative organozincs **1a,b** can couple directly with several allylic bromides giving rise to the corresponding 1,4-dienes. The geometry of the double bond on both coupling partners is conserved. Substituents on the γ-carbon of the allylic halide such as a methoxycarbonyl or a nitrile group have an effect of reducing the cross-coupling reaction yield. γ,γ-Disubstituted allylic bromides such as prenyl and geranyl bromide appear to be incompatible with these reaction conditions. In both examples, the cross-coupling product was accompanied by several other unidentified products.[19] On the basis of the last observation, and the fact that in the reaction with cinnamyl bromide both the S_N2' substitution product and the cross-coupling products **5** and **6** were also formed (even though only in traces), we could say that this reaction (under this set of conditions) is sensitive to steric effects.

In our effort to find more satisfactory reaction conditions, especially for the γ,γ-disubstituted allylic bromides,

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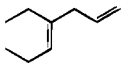
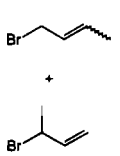
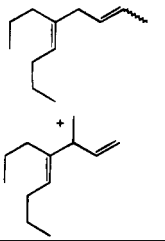
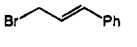
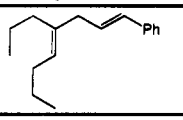
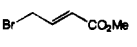
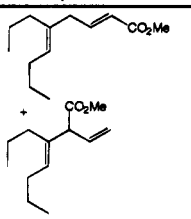
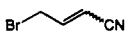
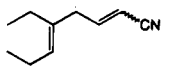
(18) Agrios, K. A.; Srebnik, M. *J. Organomet. Chem.* **1993**, *444*, 15.

(19) The ^{1}H and ^{13}C NMR spectra of the samples obtained after passing the crude products through an alumina column (elution with hexanes) were complex. However, we were able to conclude that both regioisomers, S_N2 and S_N2', along with some other unidentified products had been formed in these two reactions.

Table 1. Products Obtained by the Cross-Coupling Reaction of ((*E*)-1-Alkenyl)ethylzincs, Prepared by a Boron–Zinc Transmetalation, with Allylic Bromides in the Absence of Catalyst[a]

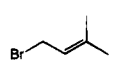
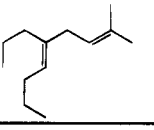
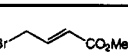
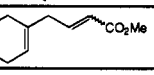
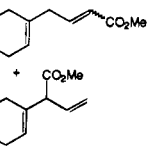
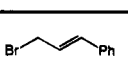
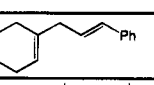
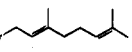
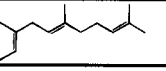
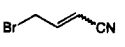
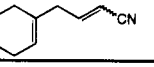
entry	zinc reagent 1	allylic bromide	product(s)[b]	yield[c]
1	1a			(98)
2	1b			(76)
3	1b			(74)
4	1b			21 (60)
5	1a			19

[a] The reaction takes place at 25 °C and goes to completion in a short period of time (10–20 min), using DMF as solvent, while the stoichiometry between the organozinc species and allylic bromide is 1:1. [b] For the ratios of geometrical and positional isomers see text. [c] The yields in parentheses are GC crude yields, while the rest of them are isolated yields.

we attempted some of these reactions in the presence of 2 mol % of a Pd(0) catalyst. The catalyst was prepared *in situ* from $Pd_2(DBA)_3$ and PPh_3 in an 1:4 ratio. The use of this catalyst has a dramatic effect on the coupling reactions involving prenyl and geranyl bromide as allylic partners. In fact, the corresponding S_N2 substitution coupling products, (2,5*E*)-2-methyl-5-propylnonadiene and (2,6*E*,9*E*)-2,6-dimethyl-9-ethyldodecatriene, were obtained in much better yields this time, and no γ-attack products were formed.

Under Pd catalysis, methyl 4-bromocrotonate showed a different behavior, as far as the regioselectivity is concerned. In particular, a solvent effect on the regiochemistry of the coupling reaction of methyl 4-bromocrotonate with organozinc **1a** became apparent. In the presence of DMF (Table 2, entry 3), both regioisomeric 1,4-dienes were formed in a 2:1 ratio, again in favor of the S_N2 coupling product (according to GC analysis of the crude product), while in the presence of THF (Table 2, entry 2), (2*E*,5*E*)-5-ethyloctadienoic methyl ester was formed exclusively. Unfortunately, the use of catalyst resulted in partial *E*/*Z* isomerization of the double bond on the allylic partner in both cases. GC analysis of the crude products showed that the ratio of the two geometrical isomers was 5:1 in THF, and 6:1 in DMF, in favor of the *E*,*E* isomer. However, the yield of the cross-coupling product improved, although not drastically (compare entries 4 and 2 of Tables 1 and 2, respectively).

Table 2. Products Obtained by the Cross-Coupling Reactions of ((*E*)-1-Alkenyl)ethylzincs, Prepared by a Boron–Zinc Transmetalation, with Allylic Bromides in the Presence of 2 mol % Catalyst, $Pd(PPh_3)_2$[a]

entry	zinc reagent 1	allylic bromide	solvent	product(s)[b] 2	% yield[c]
1	1b		THF		46 (75)
2[d]	1a		THF		40
3	1a		DMF		(84)
4	1a		THF		48
5	1a		THF		59
6	1a		THF		21

[a] The reaction takes place at 25 °C and goes to completion in a short period of time (20 min), with 2 mol % of Pd(0) catalyst (generated *in situ* as described in the Experimental Section), while the stoichiometry between the organozinc species and the allylic bromide is 1:1. [b] For the ratios of geometrical and positional isomers see text. [c] All yields are isolated, except those in parentheses, which are GC crude yields. [d] The isolated yields for the two geometrical isomers, (2*E*,5*E*)- and (2*Z*,5*E*)-5-ethyloctadienoic acid methyl ester, were 35 and 5%, respectively.

Similarly, during the cross-coupling reaction of **1a** with cinnamyl bromide (THF), the S_N2 substitution product was formed exclusively. Besides that, no cross-coupling products derived from competitive ethyl transfer (**5** and **6**) were obtained this time.

This solvent effect is not yet well understood since it was not observed consistently. For example, in the cross-coupling reaction of **1a** with 4-bromocrotononitrile (*Z*/*E*), 55:45), only one regioisomer was obtained, that with the least-substituted carbon in the allylic skeleton. The same result occurred under both sets of reaction conditions (DMF as solvent, no catalyst; and DMF or THF as solvent, in the presence of catalyst). Furthermore, in the cross-coupling reaction of prenyl bromide with **1a**, the S_N2 substitution product was formed exclusively, even when DMF was used as solvent.

In conclusion, we have shown that ((*E*)-1-alkenyl)-ethylzincs, generated from the corresponding (*Z*)-trialkenylboranes, can undergo direct coupling with certain allylic halides, in DMF, to provide stereodefined 1,4-dienes. To our knowledge, there are no examples in the literature of vinyl organometallic species which can couple with allylic electrophiles in the absence of a transition metal catalyst.[9–13] The use of a coordinatively unsaturated palladium(0) catalyst changes the course of this reaction. The catalyst appears to be absolutely critical for the reactions involving prenyl and geranyl bromide as the allylic partners. In the case of methyl 4-bromocrotonate, the effect of the specific catalyst on the reaction yield is not so profound. However, in combination with the use of the appropriate solvent (THF), the

presence of the catalyst results in total elimination of the γ-attack coupling product, formed under conditions of direct coupling.

Experimental Section

Glassware, syringes, and needles were oven-dried at 120 °C, assembled while hot, and dried under a flow or Ar. All reactions were done under a positive pressure of Ar.[20] The alkenylboranes **3** were obtained from the corresponding alkynes by reaction with BH_3·Me_2S in CH_2Cl_2.[21] Solutions of tri-(*Z*)-3-hexenylborane and tri-(*Z*)-4-octenylborane in hexanes (1 M) were prepared and used in all the reactions. Diethylzinc was purchased from Ethyl Corp. and used as such to make a 2 M solution in hexanes. All solvents were dried and distilled prior to use, hexanes and THF from sodium, and DMF by azeotropic distillation from benzene. The alkynes were purchased from Farchan, and the allylic halides,[22] as well as the Pd catalyst, were purchased from Aldrich. The alkynes were distilled from CaH_2 prior to use. The allylic halides were also distilled and stored in ampoules under Ar. GC analysis was done on a SE-30 (0.25-mm i.d.) capillary column. ^1H and ^{13}C NMR spectra are of $CDCl_3$ solutions. TMS served as an internal standard. Mass spectra were obtained on a GC/MS, fitted with a 25 m methylsilicone capillary column.

General Procedure for the Cross-Coupling of ((*E*)-1-Alkenyl)ethylzincs with Allylic Bromides in the Absence of Catalyst. Preparation of (1*E*,4*E*)-1-Phenyl-4-propyloctadiene. A 25-mL round-bottom flask fitted with a side-arm, Teflon-lined stirring bar, and gas-regulating valve was charged under Ar with tri-(*Z*)-4-octenylborane (1 M in hexanes, 1 mL, 1 mmol), after which the hexanes were removed under reduced pressure. To the borane was added via syringe 1 mL of DMF, followed by the addition of diethylzinc (2 M in hexanes, 1.5 mL, 3 mmol). The solution was allowed to equilibrate at 25 °C for 10 min, after which a solution of cinnamyl bromide (0.6 g, 3 mmol) in 1 mL of DMF was added dropwise via a double-ended needle. The reaction is exothermic. After a period of 20 min the formed BEt_3 was removed under reduced pressure, and the remaining reaction mixture was quenched with HCl(aq), followed by extraction with ether. The organic phase was washed successively with H_2O, NaOH(aq), and HCl(aq) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash column chromatography on alumina (elution with hexanes) gave 0.31 g of a colorless liquid (see text regarding purity of this sample): ^1H NMR ($CDCl_3$) δ 7.36–7.27 (3H, m), 7.19 (2H, t, J = 7.1 Hz), 6.38 (1H, d, J = 15.7 Hz), 6.19 (1H, dt, J = 15.8, 7.0 Hz), 5.22 (1H, t, J = 7.1 Hz), 2.87 (2H, d, J = 7.0 Hz), 2.05–1.97 (4H, m), 1.44–1.34 (4H, m), 0.92–0.88 (6H, m); ^{13}C NMR ($CDCl_3$) δ 137.8, 130.7, 129.5, 128.4, 126.8, 126.5, 126.0, 40.6, 32.3, 30.0, 23.2, 21.5, 14.1, 13.9; GCMS (*m/z*) 228 (M^+), 226, 183, 170, 142, 128, 90, 80.

(1,4*E*)-4-Ethylheptadiene. The reaction was run as above with **1a**, except that allyl bromide (0.26 mL, 0.36 g, 3 mmol) was used. The reaction mixture was worked up as described above, and the crude sample obtained was subjected to GCMS analysis: GC crude yield, 98%; GCMS (*m/z*) 124 (M^+), 109, 95, 83, 67, 55, 41, 39.

Mixture of (2*E*,5*E*) and (2*Z*,5*E*)-5-Propylnonadiene and (1,4*E*)-3-methyl-4-propyloctadiene. The reaction was run as above with **1b**, except that crotyl bromide (0.31 mL, 0.41 g, 3 mmol, mixture of isomers(see text)) was used. A small amount of the crude product (50 mg) was dissolved in ether and loaded on a silica gel TLC plate (elution with hexanes). The band corresponding to the coupling products was scraped off the TLC plate and dissolved in ether. After the solvent was removed under reduced pressure, a pure analytical sample (containing all isomers) was obtained: GC crude yield (76%).

(20) For details on working with air-sensitive materials using syringe techniques see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Organoboranes*; Wiley: New York, 1975; p 191.

(21) Brown, H. C.; Zaidlewicz, M. in *Inorganic Reactions and Methods*; *Zuckerman*, J. J.; Hagen, A. P., Eds.; VCH: Deerfield Beach, 1989; Vol. 10, Chapter 5.3; p 35.

(22) 4-Bromocrotononitrile was prepared from crotononitrile, mixture of *E* and *Z* isomers (*E*/*Z*), according to the procedure described in: Bailey, W. J.; Bello, J. *J. Org. Chem.* **1955**, *20*, 525.

(2*E*,5*E*)-5-Propylnonadienoic Acid Methyl Ester and (3*E*)-2-Ethenyl-3-propylheptenoic Acid Methyl Ester (72:28). The reaction was run as above with **1b**, except that methyl 4-bromocrotonate (0.35 mL, 0.54 g, 3 mmol) was used. Two regioisomers were formed in a 72:28 ratio (based on GC analysis of the crude product, GC crude yield, 60%). Flash column chromatography on alumina (elution with ether/hexanes (3:97)) gave 0.13 g (21%) of pure product (both regioisomers) as a colorless liquid. A pure analytical sample of each regioisomer was obtained by preparative TLC (silica gel, ether/hexanes (5:95)); (2*E*,5*E*)-5-propylnonadienoic acid methyl ester: ^1H NMR ($CDCl_3$) δ 6.93 (1H, dt, J = 15.5, 7.2 Hz), 5.80 (1H, d, J = 15.6 Hz), 5.16 (1H, t, J = 7.2 Hz), 3.71 (3H, s), 2.83 (2H, d, J = 7.2 Hz), 1.99–1.93 (4H, m), 1.38–1.30 (4H, m), 0.87 (3H, t, J = 7.3 Hz), 0.86 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.1, 148.2, 135.6, 128.1, 121.6, 51.4, 39.7, 32.3, 30.0, 23.0, 21.4, 14.0, 13.9; GCMS (*m/z*) 210 (M^+), 179, 167, 153, 121, 107, 93, 79, 69, 55; (3*E*)-2-ethenyl-3-propylheptenoic acid methyl ester: ^1H NMR ($CDCl_3$) δ 6.01–5.92 (1H, m), 5.29 (1H, t, J = 7.1 Hz), 5.12–5.05 (2H, m), 3.66 (3H, s), 3.62 (1H, d, J = 8.4 Hz), 2.03–1.96 (4H, m), 1.41–1.31 (4H, m), 0.873 (3H, t, J = 7.3 Hz), 0.867 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 136.3, 135.6, 128.6, 116.8, 56.2, 51.9, 32.1, 30.0, 22.8, 21.7, 14.1, 13.8; GCMS (*m/z*) 210 (M^+), 167, 151, 121, 111, 109, 107, 100, 95, 91, 79, 77, 69, 67, 59, 55.

Mixture of (2*E*,5*E*) and (2*Z*,5*E*)-5-Ethyloctadienonitrile. The reaction was run with **1a** as above, except that 4-bromocrotononitrile, a mixture of *E* and *Z* isomers (0.44 g, 3 mmol, *E*/*Z*, 45:55) was used. Pure product (colorless liquid) was obtained by flash column chromatography on silica gel (elution with ether/hexanes, (4:96)): yield 85 mg (19%); the *E*/*Z* ratio in the crude coupling product was 50:50, based on integration of the ^1H NMR signals corresponding to the double allylic protons of both isomers: ^1H NMR ($CDCl_3$) δ 6.72 (1H, dt, J = 16.4, 6.9 Hz), 6.48 (1H, dt, J = 10.9, 7.8 Hz), 5.37–5.32 (1H, m), 5.18–5.12 (1H, m), 3.09 (2H, d, J = 7.7 Hz), 2.87 (2H, d, J = 7.0 Hz), 2.07–1.98 (4H, m), 1.02–0.93 (6H, m); ^{13}C NMR ($CDCl_3$) δ 154.5, 153.6, 136.1, 135.6, 130.1, 129.2, 117.6, 116.0, 100.3, 99.8, 40.2, 38.8, 23.3, 23.2, 21.0, 20.9, 14.4, 13.0; GCMS (*m/z*) 149 (M^+), 133, 119, 105, 82, 79, 55, 41.

General Procedure for the Cross-Coupling of ((*E*-1-Alkenyl)ethylzincs with Allylic Bromides in the Presence of a Palladium(0) Catalyst. Preparation of (2,6*E*,9*E*)-2,6-Dimethyl-9-ethyldodecatriene. A 50-mL round-bottom flask fitted with a side-arm, Teflon-lined stirring bar, and gas-regulating valve was charged under argon with 0.60 mL (0.65 g, 3 mmol) of geranyl bromide, followed by the addition of 5 mL of THF. To the solution was added successively 32 mg (0.12 mmol) of PPh_3 and 28 mg (0.03 mmol) of $Pd_2(DBA)_3$. The mixture was stirred for a period of 10–15 min, when a homogeneous yellow solution was obtained. Prior to this procedure, a 25-mL round-bottom flask, also fitted with a side-arm, Teflon-lined stirring bar, and gas-regulating valve was charged under Ar with tri-(*Z*)-3-hexenylborane (1 M in hexane, 1 mL, 1 mmol). After removing the hexanes under reduced pressure, 1 mL of DMF was added to the borane, followed by the addition of diethylzinc (2 M in hexane, 1.5 mL, 3 mmol). The solution was allowed to equilibrate at 25 °C for 10 min, and then it was transferred dropwise via a double-ended needle to the 50-mL round-bottom flask, containing the solution of geranyl bromide and the palladium(0) catalyst. After a period of 20 min, the formed BEt_3 was removed under reduced pressure, and the remaining reaction mixture was quenched with HCl(aq), followed by extraction with ether. The organic phase was washed successively with H_2O, NaOH(aq), and HCl(aq) and finally dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash column chromatography on alumina (elution with hexanes) gave 0.39 g (59% based on geranyl bromide) of pure product as a colorless liquid: ^1H NMR ($CDCl_3$) δ 5.16–5.07 (3H, m), 2.68 (2H, d, J = 7.1 Hz), 2.12–1.97 (8H, m), 1.68 (3H, s), 1.61 (6H, s broad), 0.98–0.92 (6H, m); ^{13}C NMR ($CDCl_3$) δ 139.8, 135.8, 131.3, 125.9, 124.4, 122.9, 39.8, 35.1, 26.7, 25.7, 23.3, 20.9, 17.7, 15.9, 14.8, 13.3; GCMS (*m/z*) 219, 218, 203, 189, 150, 135, 122, 108, 94, 80, 68.

(2*E*,5*E*)-5-Ethyloctadienoic Acid Methyl Ester. The reaction was run with **1a** as above, except that methyl 4-bromocrotonate (2.35 mL, 3.58 g, 20 mmol) was used. Pure product (colorless liquid) was obtained by flash column chromatography

on alumina (elution with ether/hexanes, (3:97)): yield 1.27 g (35%); ^{1}H NMR ($CDCl_3$) δ 6.96 (1H, dt, J = 15.6, 7.2 Hz), 5.83 (1H, d, J = 15.6 Hz), 5.14 (1H, t, J = 7.2 Hz), 3.73 (3H, s), 2.86 (2H, d, J = 7.0 Hz), 2.05–1.99 (4H, m), 0.95 (6H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.1, 148.1, 136.8, 129.0, 121.6, 51.4, 39.3, 23.2, 21.0, 14.5, 13.1; GCMS (*m/z*) 182 (M^+), 180, 152, 138, 122, 92, 82, 54. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.60; H, 10.30.

The (2*Z*,5*E*) isomer (0.19 g, 5%) was also isolated in this reaction. During the column chromatography process, we observed the existence of one additional compound in the early fractions containing the desired product. After removal of the solvent, the ^{1}H NMR spectrum of the residue showed the following peaks indicative of the (2*Z*,5*E*) isomer: δ 6.23 (1H, dt, J = 11.6, 7.6 Hz), 3.72 (3H, s), 3.37 (2H, d, J = 7.3 Hz). In addition, the ^{13}C NMR spectrum showed the following extra peaks: δ 166.9, 149.1, 138.1, 127.9, 119.5, 51.0, 35.8, 23.5, 13.12.

(1*E*,4*E*)-4-Ethyl-1-phenylheptadiene. The reaction was run as with **1a** above, except that cinnamyl bromide (0.6 g, 3 mmol) was used. Pure product (colorless liquid) was obtained by flash column chromatography on alumina (elution with hexanes): yield 0.29 g (48%); ^{1}H NMR ($CDCl_3$) δ 7.37–7.35 (2H, m), 7.31–7.27 (2H, m), 7.19 (1H, t, J = 7.2 Hz), 6.39 (1H, d, J = 15.8 Hz), 1H, dt, J = 15.8, 7.1 Hz), 5.18 (1H, t, J = 7.1 Hz), 2.88 (2H, d, J = 7.0 Hz), 2.09–2.00 (4H, m), 1.00–0.94 (6H, m); ^{13}C NMR ($CDCl_3$) δ 139.0, 137.8, 130.8, 129.4, 128.5, 127.4, 126.9, 126.0, 40.3, 23.2, 21.0, 14.7, 13.2; GCMS (*m/z*) 200 (M^+), 198, 170, 142, 128, 108, 90, 66, 43.

(2,5*E*)-2-Methyl-5-propylnonadiene. The reaction was run with **1a** as above, except that prenyl bromide (0.35 mL, 0.45 g, 3 mmol) was used. Pure product (colorless liquid) was obtained by flash column chromatography on alumina (elution with hexanes): yield 0.25 g (46%); ^{1}H NMR ($CDCl_3$) δ 5.11 (2H, t, J = 7.3 Hz), 2.63 (2H, d, J = 7.3 Hz), 1.97–1.92 (4H, m), 1.70 (3H, s), 1.59 (3H, s), 1.40–1.29 (4H, m), 0.87 (5H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 138.6, 132.2, 125.0, 123.0, 35.6, 32.3, 29.9, 25.8, 23.2, 21.6, 17.6, 14.2, 13.9; GCMS (*m/z*) 152 (M^+), 136, 122, 108, 95, 80, 66, 54.

(2*E*,5*E*)- and (2*Z*,5*E*)-5-Ethyloctadienonitrile. The reaction was run with **1a** as above except that 4-bromocrotononitrile, a mixture of *E* and *Z* isomers, (0.44 g, 3 mmol, *E*/*Z*, 45:55), was used. Flash column chromatography on alumina (elution with ether/hexanes, 4:96) gave 0.050 g of (2*Z*,5*E*)-5-ethyloctadienonitrile and 0.044 g of (2*E*,5*E*)-5-ethyloctadienonitrile (21% combined yield) as colorless liquids; (2*Z*,5*E*)-5-ethyloctadienonitrile: ^{1}H NMR ($CDCl_3$) δ 6.48 (1H, dt, J = 10.9, 7.8 Hz), 5.36 (1H, d, J = 10.8 Hz), 5.16 (1H, t, J = 7.3 Hz), 3.09 (2H, d, J = 7.7 Hz), 2.07–1.99 (4H, m), 1.00 (3H, t, J = 7.6 Hz), 0.95 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 153.6, 136.1, 129.2, 116.0, 99.8, 38.8, 23.3, 20.9, 14.4, 13.0; GCMS (*m/z*) 149 (M^+), 133, 119, 105, 82, 79, 55, 41; (2*E*,5*E*)-5-ethyloctadienonitrile: ^{1}H NMR ($CDCl_3$) δ 6.72 (1H, dt J = 16.4, 6.9 Hz), 5.34 (1H, dt, J = 16.4, 1.6 Hz), 5.14 (1H, t, J = 7.3 Hz), 2.87 (2H, d, J = 7.0 Hz), 1.07–1.98 (4H, m), 0.96 (3H, t, J = 7.5 Hz), 0.95 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 154.5, 135.6, 130.1, 117.6, 100.3, 40.2, 23.2, 21.0, 14.4, 13.0; GCMS (*m/z*) 149 (M^+), 133, 119, 105, 82, 79, 55, 41.

Acknowledgment. The University of Toledo is thanked for financial support, the State of Ohio Academic Challenges Program for a high-field NMR spectrometer, and the U. S. Department of Education for a cost-sharing grant for the purchase of a GC/MS/DS instrument.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for products in Tables 1 and 2 (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.