Stereocontrolled Synthesis of 6-*s*-*cis*- and 6-*s*-*trans*-Locked 9*Z*-Retinoids by Hydroxyl-Accelerated Stille Coupling of (*Z*)-Tri-*n*-Butylstannylbut-2-en-1-ol and Bicyclic Dienyl Triflates

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Analogues of 9-*cis*-retinoic acid with locked 6-*s*-*cis* and 6-*s*-*trans* conformations have been stereoselectively synthesized using a Stille coupling reaction between bicyclic dienyl triflates (**5** and **6**, respectively) and (*Z*)-tributylstannylbut-2-en-1-ol (**7**) to stablish the *Z* geometry of the polyenic side chain. The mild conditions (25 °C, 30 min) of this coupling stand in contrast to the reluctance of the isomeric (*E*)-tributylstannylbut-2-en-1-ol (**18**) to react with triflates **5**/**6**. The significant rate differences experimentally observed in Stille reactions between isomeric (*Z*)- and (*E*)-tri-*n*-butylstannylalkenols in favor of the former isomer, even with highly hindered alkenyl triflates, is ascribed to internal coordination of palladium to the heteroatom in the presumably rate-limiting transmetalation step. Dienals and trienals with an *E* geometry, which are not efficiently available by direct coupling of the corresponding triflates and *E*-stannanes, can in turn be obtained by isomerization of their *Z*-isomers.

Introduction

Retinoids, i.e., the natural and synthetic analogues of vitamin A,[1,2] act as modulators of nuclear transcription by binding to and activating two subfamilies of nuclear receptors,[3] namely the RXRs,[4] which use 9-*cis*-retinoic acid (**1**, Figure 1) as native ligand, and the RARs,[5] activated by both 9-*cis*-retinoic acid (**1**) and *trans*-retinoic acid (**2**). This activation results in regulation of important cellular processes such as cell differentiation and proliferation, morphogenesis, development, hematopoyesis, and immune function.[1] Although detailed crystal structures are available for several members of the nuclear receptor superfamily,[6] including the unbound RXRα,[6c] no data is yet available for the ligand-bound RXRα protein. We therefore set out to explore the conformation of the ligand on binding RXRα by locking specific bonds within cyclic structures. In particular the C6−C7 bond, controlling the relative orientation of the polyenic side chain and the hydrophobic ring, might play a major role on the binding and activation of RXR by its cognate ligand 9-*cis*-retinoic acid (**1**). A similar strategy has been extremely useful in retinal protein research, with the use of designed analogues to study the conformation and/or configuration that the polyene side chain adopts on the different states of the photocycles triggered by light on the membrane proteins rhodopsin and bacteriorhodopsin.[7] Two limiting conformations of the C6−C7 bond, 6-*s*-*trans* and 6-*s*-*cis*, could be locked by means of a methyl-

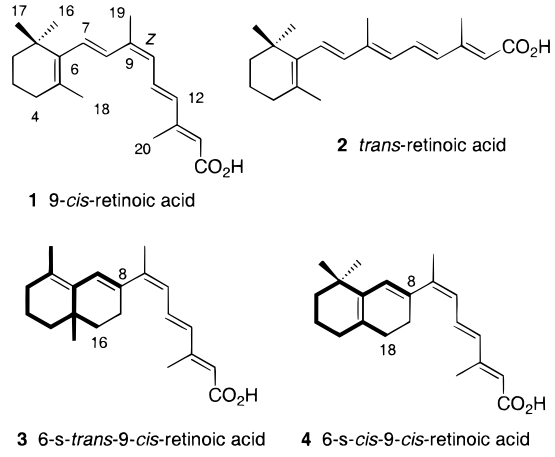

Figure 1.

(1) (a) *The Retinoids*; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Academic Press: New York, 1984; Vols. 1 and 2. (b) *The Retinoids: Biology, Chemistry and Medicine*, 2nd ed.; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven: New York, 1993. (c) *Retinoids: New Trends in Research and Therapy*; Saurat, J. H., Ed.; Karger: Basel, 1985. (d) *Retinoids and Cell Differentiation*; Sherman, M. I., Ed.; CRC Press: Boca Raton, FL, 1986. (e) *Chemistry and Biology of Synthetic Retinoids*; Dawson, M. L., Okamura, W. H., Eds.; CRC Press: Boca Ratón, FL. 1990. (f) *Methods in Enzymology;* Packer, L., Ed.; Academic Press: New York, 1990; Vol. 89, Retinoids Part A. (g) *Methods in Enzymology*; Packer, L., Ed.; Academic Press: New York, 1991; Vol. 90, Retinoids Part B. (h) *From Molecular Biology to Therapeutics*; Pharmacol. Skin; Bernard, B. A., Shroot, B., Eds.; Karger: Basel, 1993. (i) *Retinoids: From Basic Science to Clinical Applications*; Livrea, M. A., Vidali, G., Eds.; Karger: Basel, 1994.

(2) For details on the nomenclature and numbering of retinoids, see: IUPAC−IUB Joint Commission on Biochemical Nomenclature (JCBN), *Eur. J. Biochem*. **1982**, *129*, 1−5.

(3) (a) Mangelsdorf, D. J.; Thummel, C.; Beato, M.; Herrlich, P.; Schütz, G.; Umesono, K.; Blumberg, B.; Kastner, P.; Mark, M.; Chambon, P.; Evans, R. M. *Cell* **1995**, *83*, 835−839. (b) Mangelsdorf, D. J.; Evans, R. M. *Cell* **1995**, *83*, 841−850.

(4) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R: M.; Thaller, C. *Cell* **1992**, *68*, 397−406.

(5) Petkovich, M.; Brand, N. J.; Kurst, A.; Chambon, P. *Nature* **1987**, *330*, 444−450.

(6) (a) Wurtz, J.-M.; Bourguet, W.; Renaud, J.-P.; Vivat, V.; Chambon, P.; Moras, D.; Gronemeyer, H. *Nature Struct. Biol.* **1996**, *3*, 87−94 (canonical structure). (b) Renaud, J.-P.; Rochel, N.; Ruff, M.; Vivat, V.; Chambon, P.; Gronemeyer, H.; Moras, D. *Nature* **1995**, *378*, 681−689. (RARγ-holo-LBD). (c) Bourguet, W.; Ruff, M.; Chambon, P.; Gronemeyer, H.; Moras, D. *Nature* **1995**, *375*, 377−382. (hRXRα). (d) Wagner, R. L.; Apriletti, J. W.; McGrath, M. E.; West, B. L.; Baxter, J. D.; Fletterick, R. J. *Nature* **1995**, *378*, 690−697. (hTRα1-holo-LBD).

(7) Nakanishi, K.; Crouch, R. *Isr. J. Chem*. **1995**, *35*, 253−272.

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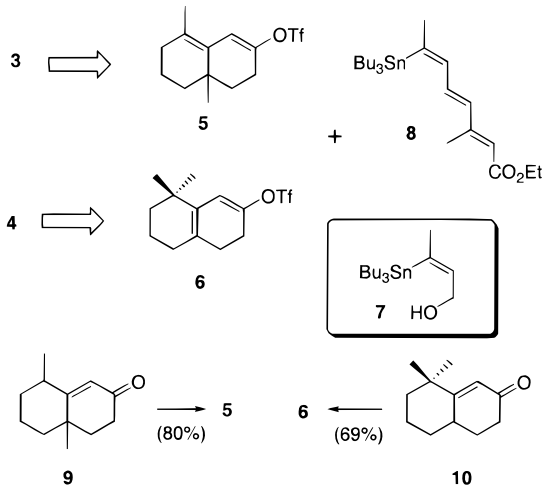
Scheme 1[a]



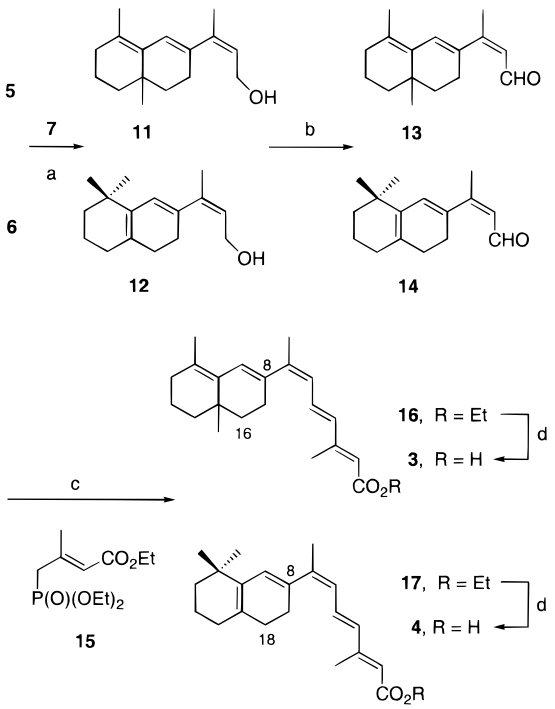
[a] Reagents and conditions: Tf_2O, DBMP, CH_2Cl_2, 25 → 50 °C.

ene unit bridging C8 and C16 (analogue **3**), and C8 and C18 (analogue **4**), respectively. The stereocontrolled synthesis of these designed analogues is described in this article. It features a Stille coupling between dienyl triflates **5** or **6**, and stannane **7** (Scheme 1), which takes place under mild reaction conditions [$Pd_2(dba)_3$ (2.5 mol %) and $AsPh_3$ (20 mol %) in NMP, 25 °C, 30 min]. Since isomeric stannane **18** coupled to dienyl triflate **5** more sluggishly (50 °C, 16 h), it was confirmed that Stille couplings involving **7** and related *Z*-tri-*n*-butylstannylalkenols enjoyed a rate-acceleration effect induced by complexation of the hydroxyl group to the metal, an effect which also facilitates their coupling with highly hindered alkenyl triflates, and these results are also reported.

Results and Discussion

Dienyltriflates **5** and **6** are easily accessible in good yield (80% for **5**, 69% for **6**) from the corresponding bicyclic ketones **9**[8] and **10**,[9] respectively, by treatment with Tf_2O in the presence of di-*tert*-butylmethylpyridine (DBMP), a combination previously developed for the synthesis of esteroidal ketones.[10] We first explored a direct and convergent approach involving the Stille coupling[11,12] of **5** and stereochemically homogeneous trienylstannane **8**.[13] However, temperatures of 40 °C were required even using the recent modifications of the catalyst, with ligands of lower affinity toward Pd(II) [triphenylarsine and tri(2-furyl)phosphine].[14] Under these conditions, double bond isomerization with loss of stereochemical integrity of the labile cis double bond could not be avoided (Scheme 2). A stepwise construction of the polyene skeleton was alternatively sought. Gratifyingly, (*Z*)-3-tributylstannylbut-2-en-1-ol (**7**)[15a] coupled to triflates **5** and **6** at ambient temperature under the optimized conditions reported by Farina [$Pd_2(dba)_3$ (2.5 mol %) and $AsPh_3$ (20 mol %) in NMP][14a] after only 30 min, providing trienes **11** and **12**, respectively, in 95% yield (Scheme 2). The sensitive trienals **13** and **14**, which are prone to double-bond isomerization upon attempted oxidation of **11** and **12** with MnO_2 or TPAP/NMO, were nevertheless obtained from **11** and **12** with the Dess−Martin reagent.[16] Without manipulation, aldehydes **13** and **14** were subjected to Horner−Wadsworth−Emmons condensation with the anion derived from phosphonate **15** and BuLi in the presence of DMPU at −78 °C,[17] leading to pentaenes **16**

Scheme 2[a]



[a] Reagents and conditions: (a) 2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$, NMP, 25 °C, 0.5 h (95% for **11**, 95% for **12**); (b) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C, 5 min (69% for **13**, 65% for **14**); (c) *n*-BuLi, DMPU, THF, 0 °C, 20 min; then aldehyde **13** or **14**, −78 °C (70% for **16**, 77% for **17**); (d) 5 N KOH, EtOH, reflux, 0.5 h (77% for **3**, 95% for **4**).

(8) Still, W. C.; VanMiddlesworth, F. L. *J. Org. Chem.* **1977**, *42*, 1258−1259.

(9) Takahashi, K.; Suzuki, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 4603−4604.

(10) (a) Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438−440. (b) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *Tetrahedron Lett.* **1988**, *29*, 1581−1582. (c) Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I. *J. Am. Chem. Soc.* **1989**, *111*, 278−284.

(11) (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771−1780. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: Oxford, 1995; Vol. 12, chapter 3.4, pp 161−241. (d) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: New York, 1996; Vol. 5, pp 1−53. (e) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, chapter 1, pp 1−652. (f) Farina, V.; Krishnamurthy, V. *The Stille Reaction*; Wiley: New York, 1999.

(12) For recent work into the mechanism of the Stille coupling reaction, see: (a) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954−959. (b) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978−8985. (c) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.

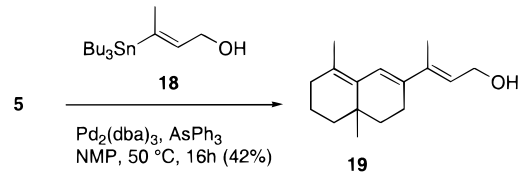
(13) Stannyltrienoate **8** was synthesized from stannyl aldehyde **40** (Scheme 4) and phosphonate **15** (Scheme 2).

(14) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (b) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243−4246. (c) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434−5444.

(15) (a) Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173−1176. (b) Elbaum, D.; Porco, J. A.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 211−225. (c) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6559−6562.

(16) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (e) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272−7276.

Scheme 3



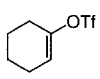
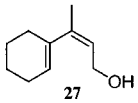
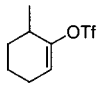
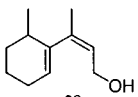
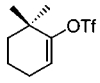
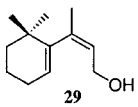
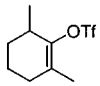
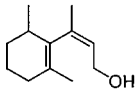
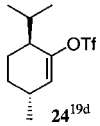
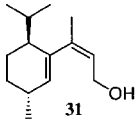
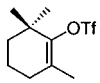
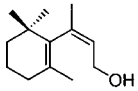
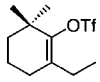
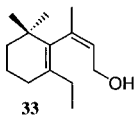
and **17**, respectively, in good yield and with excellent stereocontrol. Saponification of esters **16** and **17** finally led to the desired targets **3** and **4**, respectively, without compromising the stereochemical integrity of the polyene side chain (Scheme 2).

The mild conditions and high yields of the combinations between dienyl triflates **5**/**6** and stannane **7** were at first striking, since it is known that the Stille coupling is very sensitive to steric hindrance, and the coupling of geminal-substituted alkenyl fragments (stannane and triflate) to provide an internal substituted Csp^2-Csp^2 single bond is usually nonefficient.[11] To prove this assertion, the coupling of isomeric (*E*)-3-tributylstannylbut-2-en-1-ol (**18**) with dienyl triflate **5** required instead heating to 50 °C for 16 h and provided trienol **19** in a dissapointing 42% yield (Scheme 3).

This divergent kinetic behavior led us to search for the structural factors responsible for the significant rate differences exhibited by stannylalkenols differing in alkene geometry. To this end, and in order to explore the steric tolerance of the Stille reaction, readily available cyclohexenyl triflates[18] were selected as electrophilic partners in the coupling reactions. Although unhindered alkenyl triflates are among the most reactive electrophiles, their reactivity can be modulated by neighboring alkyl substitution and/or allylic strain.[18] These analogues are easily obtained from cyclic ketones with various substitution patterns, and procedures have been developed allowing the regioselective synthesis of either kinetic or thermodynamic triflate.[18,19] The cyclic nature of the triflates greatly simplifies the analysis, since the potential complications due to substrate and/or product isomerization are minimized and restricted to the alkene derived from the organostannane component. Triflates **20**−**26** (shown in Table 1) were thus prepared from the precursor ketones using Ph_2NTf or Tf_2O as the triflating agent with an appropriate base.[19]

The coupling of **7** to unhindered triflates proceeded quickly and efficiently (entries 1 and 2, Table 1) at room temperature with short reaction times, and only upon increasing the steric bulk in the proximity of the carbon−triflate bond (cis or allylic positions) are longer reaction times required (entries 3−7). Even triflate **25**,[19a] which is particularly sluggish in cross-coupling reactions,[20] coupled to **7** at room temperature, the reaction requiring 72 h to reach completion. The more hindered ethyl

Table 1. Stille Reactions of Alkenyl Triflates and Alkenyl Stannane 7

Entry[a]	Triflate	t (h)	Product	Yield (%)
1	 **20**[19c]	0.25	 **27**	80
2	 **21**[19a]	1	 **28**	76
3	 **22**[29a]	5	 **29**	84
4	 **23**[19a]	24	 **30**	70
5	 **24**[19d]	24	 **31**	85
6	 **25**[19a]	72	 **32**	56
7	 **26**[19e]	72	 **33**	41

[a] Reactions were carried out at room temperature with 2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$ as catalyst and 1:1.1 triflate/stannane **7** ratio in NMP.

derivative **26** behaved similarly (entry 7). However, the yields of dienes **32** and **33** were lower, due to product deterioration at extended reaction times. By comparison, hindered triflate **25** did not react with isomeric (*E*)-tributylstannylalkenol **18** even after heating to 100 °C.[21]

From these results, it was concluded that the hydroxyl group of **7** was facilitating the reactivity of the stannane in Stille coupling reactions, an effect which could be synthetically significant. To estimate the scope and limitations of the functional group assistance from a synthetic perspective,[22] we compared the reactivity of a series of stannanes other than **7** and **18**, with a hindered triflate such as **25**. The synthesis of the alkenylstannanes listed in Table 2 took advantage of the versatile stan-

(17) (a) Bennani, Y. L. *J. Org. Chem.* **1996**, *61*, 3542−3544. (b) Bennani, Y. L.; Boehm, M. F. *J. Org. Chem.* **1995**, *60*, 1195−1200.ç

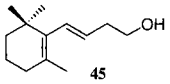
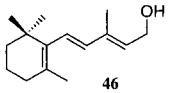
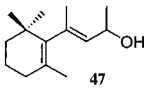
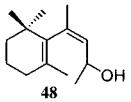
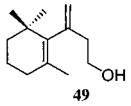
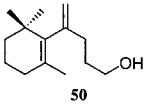
(18) For a review, see: Ritter, K. *Synthesis* **1993**, 735−762.

(19) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630−4632. (c) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283−284. (d) Preparation of **24**: Regioselective enolization of (−)-menthone by treatment with LDA in THF at −78 °C and trapping the enolate with *N*-phenyltrifluoromethanesulfonimide; see, Paquette, L. A.; Ra, C. S.; Edmonson, S. D. *J. Org. Chem.* **1990**, *55*, 2443−2445. (e) Preparation of **26**: Treatment of 6-ethyl-2,2-dimethylcyclohexanone (Hopf, H.; Krause, N. *Liebigs Ann. Chem.* **1987**, 943−947) with LDA as described in 19d above.

(20) (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (c) Roth, G. P.; Farina V.; Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191−2194.

(21) To discard that rate-acceleration was merely due to the different olefin configuration of stannanes **7** and **18**, we prepared geometrically homogeneous *E*- and *Z*-2-tri-butylstannylbutenes by trapping with $ClSnBu_3$ the anion obtained upon treatment of commercially available *E*- and *Z*-2-bromobutene with *n*-BuLi. Both stannanes were treated with hindered triflate **25** and recovered unaltered even after heating to 100 °C for prolonged reaction times (up to 24 h; some deterioration observed). Since stannanes **7** and **18** differ from the *E*- and *Z*-2-tributylstannylbutenes by the presence of the hydroxyl group, and since only **7** reacts with **25**, the effect of the heteroatom on the increased reactivity of **7** is firmly stablished.

Table 2. Stille Reactions of Hindered Alkenyl Triflate 25 and Alkenyl Stannanes

Entry[a]	Stannane	Catalyst[b]	T (°C)	t (h)	Product	Yield (%)
1	**37**	A	40	24	 **45**	40
2	**35**	A	50	5	 **46**	45
3	**44**	A	100	5	 **47**	12[c]
4	**44**	B	80	1		10[c]
5	**41**	A	60	16	 **48**	64
6	**41**	B	40	2		54
7	**40**	A	100	16		-[d]
8	**42**	A	100	16		-[d]
9	**38a**	A	50	16	 **49**	51 (60)[e]
10	**38b**	A	70	16	 **50**	25 (50)[e]
11	**38c**	A	100	16		-
12	**39**	A	100	16		-

[a] Reactions were carried out with a 1:1.1 triflate **25**/stannanne ratio in NMP at the indicated temperature. [b] A = 2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$; B = 2.5 mol % $Pd_2(dba)_3$, 3 equiv LiCl; [c] Mixture of isomers. [d] Identical result using Et_3N. [e] Yield in parentheses is based on recovered stannane. For prolonged reaction times, substrate(s) deterioration was observed.

nylcupration of alkynes (Scheme 4).[23,24] Treating 3-methylpent-4-yn-1-ol (**34**) with the "higher order" cuprate formed upon treatment of Bu_3SnLi with CuCN afforded dienylstannane **35** as described.[15c,23i,j] Using the variable regioselectivity of stannylcupration through kinetic or thermodynamic capture of the stannylcuprate intermediate[24] allowed the regioselective synthesis of either the terminal (**37**)[23a,24b] or the internal alkenylstannanes (**38a**−**c**)[23a,24b] starting from alkynols **36a**−**c**. Functional group manipulations as indicated in Scheme 4 completed the preparation of the required series of stannanes (**39**, **41**,[23f] **42**,[23f] **43**, and **44**).

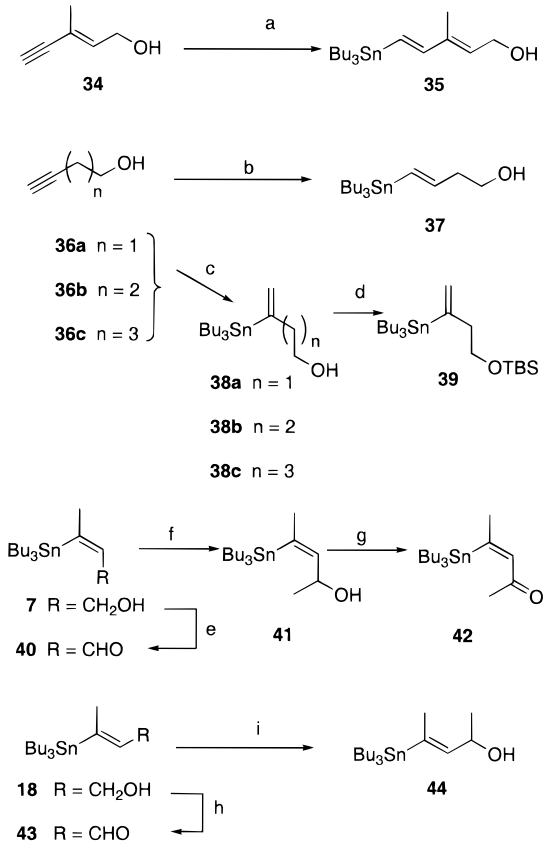
As anticipated, triflate **25** was particularly unreactive, and coupling to unhindered (*E*)-alkenylstannanes **37** and **35** required heating to 40−50 °C and provided dienol **45** and trienol **46**, respectively, in moderate yield (Table 2, entries 1 and 2). Heating to 100 °C was required for the coupling of **25** with (*E*)-4-tributylstannylpent-3-en-2-ol (**44**) (entry 3), and this reflects the greater steric hindrance in the proximity of the alkenyl carbon−tin bond. However, after 5 h the reaction mixture showed little conversion (12%) to diene **47** with 78% of the starting material being recovered. In contrast, coupling of **25** to the isomeric (*Z*)-4-tributylstannylpent-3-en-2-ol (**41**) took place at 60 °C in 16 h (entry 5) to provide diene **48** in 64% yield. The reactivity profile parallels that of terminal stannanes **37** and **35**, both of which have an *E* geometry, although these compounds benefit from the absence of the more sterically demanding methyl substituent geminal to tin, which is present in **7** and **41** (see entries 1 and 2). The rate acceleration effect of LiCl on Stille coupling reactions of alkenyl and aryl triflates[14,20] allowed the use of lower temperatures, although it did not improve the yields (see entries 4 and 6). In contrast to the behavior of (*Z*)-stannylalkenols **7** and **41**, the corresponding carbonyl derivatives **40** and **42** were recovered

(22) Although (*Z*)-3-tributylstannylpropen-1-ol was used by Stille in coupling to terminal vinyl iodides, the greater reactivity of both reaction partners [reactions proceeding at 25 °C with $PdCl_2(CH_3CN)_2$ in DMF] led to this observation remaining unnoticed. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817.

(23) (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065−2068. (b) Lipshutz, B. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 4617−4620. (c) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 327−331. (d) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253−7256. (e) Le Ménez, P.; Berque, I.; Fargeas, V.; Ardisson, J.; Pancrazi, A. *Synlett* **1994**, 998−1000. (f) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (g) Le Ménez, P.; Fargeas, V.; Berque, I.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592−3599. (h) Fargeas, V.; Le Ménez, P.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613−6634. (i) Betzer, J.-F.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1997**, *38*, 2279−2282. (j) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768−7780.

(24) (a) Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, *31*, 165−168. (b) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 770−776. (c) Singer, R. D.; Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933−4938. For a mechanistic study of the stannylcupration reactions of alkynes that show reversibility of the cuprate addition step, see: Hutzinger, M. W.; Singer, R. D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 9397−9398.

Scheme 4[a]



[a] Reagents and conditions: (a) CuCN, THF, *n*-BuLi, Bu_3SnH, THF (refs 15a, 15c, 23i, 23j); (b) (*n*-$Bu_3Sn)_2$, *n*-BuLi, CuCN, THF, 0 °C (ref 24); (c) (*n*-$Bu_3Sn)_2$, *n*-BuLi, CuCN, THF, −78 °C (**38a**, refs 23a, 24b; **38b**, ref 23c; **38c**, 62%); (d) TBSCl, imidazole, DMF, 25 °C, 5 min (92%); (e) MnO_2, CH_2Cl_2, 25 °C, 12 h (83%); (f) MeLi, THF, −78 °C, 15 min (84%); (g) Dess−Martin periodinane, pyridine, 25 °C, CH_2Cl_2 (77%); (h) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 12 h (85%); (i) MeLi, THF, −78 °C, 15 min (81%).

unaltered after heating with triflate **25** at 100 °C for 16 h (entries 7 and 8).[25]

The considerable rate-differences between isomeric alkenylstannanes strongly suggests a role for the pendant hydroxyl group in the transmetalation step, in line with the proposal of Crisp[26] and Quayle.[27] Based on these precedents, a simplified[12] yet plausible model (ignoring ligands to palladium and solvent-additives[14]) for the coupling of triflate **25** and stannane **7** (or **41**) would involve the formation of a π-complex intermediate **C**, which is chelated to palladium, following oxidative addition of Pd(0) to alkenyl triflate **25** (Figure 2). This chelation of the palladium to the oxygen and to the carbon−carbon double bond should favor transmetalation, likely the rate-limiting step of the catalytic cycle, leading to palladium (II) intermediate **D**. Reductive elimination must proceed in a straightforward manner to provide the diene product with concomitant regeneration of the catalytically active Pd(0) species.[28]

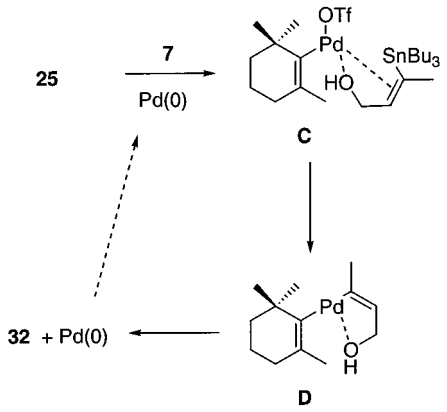
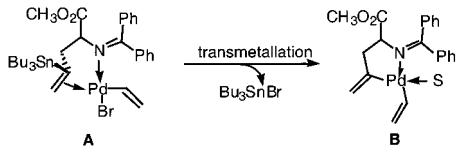


Figure 2.

The suggestion that intramolecular coordination of the heteroatom to palladium is the structural factor responsible for the rate-acceleration in the transmetalation step for coupling (*Z*)-alkenols **7** and **41** was also supported by the behavior of the generally less reactive internal alkenylstannes **38a**−**c** and **39**. An increase in reaction temperature was needed to promote the reactions of internal stannanes derived from but-3-yn-1-ol (**38a**) (50 °C, entry 9) and pent-4-yn-1-ol (**38b**) (70 °C, entry 10),

(25) β-Tributylstannyl-α,β-unsaturated ketones have been described as particularly unreactive in Stille coupling reactions, and intramolecular coordination of the carbonyl group to tin was deemed responsible for its lack of reactivity. The rate acceleration observed upon addition of Et_3N, thought to be responsible for the deactivation of the complex between tin and the carbonyl oxygen, had no effect on our system, and for this case the presumed intramolecular coordination of tin to the heteroatom did not overcome the inherent lack of reactivity exhibited by **40** and **42**. See: (a) Takeda, T.; Sugi, S.; Nakayama, A.; Suzuki, Y.; Fujiwara, T. *Chem. Lett.* **1992**, 819−822. (b) Takeda, T.; Kabasawa, Y.; Fujiwara, T. *Tetrahedron* **1995**, *51*, 2515−2524.

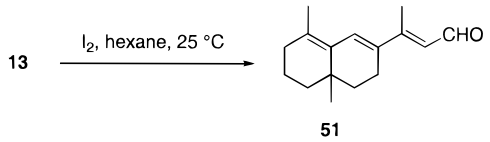
(26) In a series of studies on the regioselectivity of the Stille coupling, Crisp described a regioselective coupling of the internal stannane with a vinyl bromide starting from a mixture of both internal and terminal stannanes, which he attributed to intramolecular coordination of palladium (structures **A** and **B**) by an imine nitrogen (but not by an acetamide), only when ligandless $PdCl_2(CH_3CN)_2$ (5 mol %) was employed [see: (a) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213−3234. (b) Crisp, G. T.; Gebauer, M. G. *Tetrahedron Lett.* **1995**, *36*, 3389−3392]. In addition, $Pd_2(dba)_3$ (2.5 mol %) and $AsPh_3$ (20 mol %) in NMP retarded the coupling at the internal position, presumably due to steric factors, and favored coupling at the terminal position. We, however, did not profit from this observation, since the use of $PdCl_2(CH_3CN)_2$ (5 mol %) in the absence of ligand led to recovery of starting materials (**25** and **41**) even after heating at 100 °C for 16 h.



(27) Quayle, P.; Wang, J.; Xu, J.; Urch, C. J. *Tetrahedron Lett.* **1998**, *39*, 485−488.

(28) Alternatively, intramolecular nucleophilic assistance at tin in stannanes that incorporate a nucleophile might stabilize the transition state for transmetalation, weakening the Sn−C bond by pentacoordination, thus reacting at increased rates than in the absence of the heteroatom. For a review, see: Jastrzebski, J. T. B. H.; Van Koten, G. *Adv. Organomet. Chem.* **1993**, *35*, 241−294. Rate-accelerating effects in Stille coupling reactions due to coordination of a heteroatom to tin has been reported for alkyl and aryl transfer. Alkyl transfer: (a) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556−6558. Aryl transfer: (b) Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440−1441. However, Farina (Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78) has recently reexamined the nucleophilically assisted aryl transfer and found that is unimportant. Moreover, the nucleophilically assisted alkyl transfer is solvent dependent. The rate difference is modest but significant in dioxane and toluene (about 1 order of magnitude), whereas the effect is minor in NMP. The results suggest a change in transition state geometry from a "closed" S_E2 transition state in apolar toluene to an "open" S_E2 transition state in NMP. For recent examples of enhanced reactivity in Stille coupling reactions due to the formation of a hypervalent organotin species (which presumably accelerates transmetalation), see: (a) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5252−5243. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413.

Scheme 5



whereas that derived from hex-5-yn-1-ol (**38c**) was particularly unreactive (up to 100 °C, entry 11). However, conversions were incomplete, with recovery of starting materials in each case. The greater flexibility of larger chelates is probably responsible for their progressive lack of reactivity, the acceleration of the transmetalation step observed with the smaller ring being rapidly lost upon increasing the ring size. In addition, protection of the alcohol in **38a** as a silyl group (**39**) completely supressed the reactivity of the internal stannane (entry 12).

Summary

Despite its extended general use in organic synthesis, there is still a need to develop a better understanding of the reactivity of the Stille reaction partners. In this regard, most studies have focused on the electrophile component, and only limited studies have been reported that compare the reactivity of different stannanes.[11e,f] With the aim of expanding the utility of the Stille reaction in its application to the stereocontrolled preparation of double-bond stereoisomers of highly substituted conjugated polyenes,[29] we examined the reactivity of a series of functionalized alkenylstannanes differing in alkene geometry. We report here the finding of a considerable rate difference exhibited by (*Z*)- and (*E*)-alkenylstannanes when an alcohol group is placed cis to the carbon−tin bond, and we suggest a mechanism for the rate enhancement in the former by chelation of palladium by the heteroatom, a fact in keeping with precedent work.[26,27] The rate-acceleration effect imparted by the hydroxyl group of **7** in the key Stille reaction has been advantageously exploited in a new stereocontrolled approach to the 6-*s*-*trans*- and 6-s-*cis*-locked analogues (**3** and **4**) of 9-*cis*-retinoic acid (**1**), the native ligand of the RXR subfamily of nuclear receptors.

The above findings, besides providing stereocontrolled access to sterically hindered dienols and trienols with a terminal *Z* geometry, might have an added synthetic benefit since *Z*-tributylstannylalkenols can be used as surrogates of the less reactive *E*-isomers due to the facile isomerization of the *Z*- to the *E*-products at the carbonyl oxidation stage.[30] In particular, treating a solution of aldehyde **13** (Scheme 2) with a catalytic amount of iodine in hexane[30] afforded the *E*-isomer *E*-**13** (Scheme 5), thus overcoming the more stringent reaction conditions described in (Scheme 3) for the coupling of *E*-3-tributylstannylbut-2-en-1-ol (**18**).

Experimental Section

Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded in $CDCl_3$ or C_6D_6. The tin−proton and tin−carbon coupling constants (J_{Sn-H} and J_{Sn-C}) are given as an average of the ^{117}Sn and ^{119}Sn values. Infrared spectra (IR) were recorded in 0.1-mm path length sodium chloride cavity cells. High-resolution mass spectra (HRMS) data were recorded at an ionizing voltage of 70 eV.

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, or a 15% ethanolic phosphomolybdic acid solution. Flash chromatography was performed using E. Merck silica gel 60 (230−400 mesh).

All reactions were performed under a dry argon atmosphere in oven- and/or flame-dried glassware. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula. Solvents and reagents were distilled before use: dichloromethane from calcium hydride, and tetrahydrofuran from sodium benzophenone ketyl. "Brine" refers to saturated aqueous solution of NaCl.

***rac*-4a,8-Dimethyl-2-[(trifluoromethanesulfonyl)oxy]-3,4,4a,5,6,7-hexahydronaphthalene (5).** Trifluoromethanesulfonic anhydride (0.83 mL, 4.91 mmol) was added to a solution of *rac*-4a,8-dimethyl-3,4,4a,5,6,7,8-heptahydronaphthalen-2-one **9**[8] (0.483 g, 2.73 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.12 g, 3.46 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 12 h and then heated to 50 °C for 1 h. The reaction mixture was cooled to 0 °C and diluted with hexane. The solids were filtered, and the solvents were removed in vacuo. The residue was distilled under vacuum (110 °C; 0.3 mmHg) to afford 0.67 g (80%) of **5** as a colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.2−1.4 (m, 1H), 1.70 (s, 3H), 1.4−1.9 (m, 5H), 2.0−2.2 (m, 2H), 2.3−2.5 (m, 1H), 2.5−2.7 (m, 1H), 6.42 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.2, 18.9, 22.8, 25.5, 31.9, 32.5, 36.8, 37.0, 116.8, 129.8, 133.4, 148.0; HRMS (EI$^+$) calcd for $C_{13}H_{17}F_3O_3S$ 310.0851, found 310.0856.

***rac*-(*Z*)-3-(4a,8-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)but-2-en-1-ol (11).** A solution of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol) in NMP (2.5 mL) was treated with $AsPh_3$ (0.027 g, 0.087 mmol) and, after 5 min, a solution of triflate **5** (0.1 g, 0.323 mmol) in NMP (0.5 mL) was added. After the solution was stirred for 10 min, a solution of stannane **7** (0.172 g, 0.477 mmol) in NMP (0.5 mL) was then added. The resulting solution was stirred at 25 °C for 30 min, saturated aqueous KF solution (5 mL) was added, and the mixture was stirred for 30 min and extracted with Et_2O. The combined organic extracts were washed with H_2O and saturated aqueous KF solution, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.071 g (95%) of **11** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.1−2.4 (m), 1.68 (s, 3H), 1.85 (d, J = 1.1 Hz, 3H), 4.1−4.3 (m, 2H), 5.41 (tq, J = 6.7, 1.1 Hz, 1H), 6.06 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 18.5, 18.6, 23.0, 23.2, 25.0, 31.7, 32.8, 37.3, 37.7, 60.4, 122.5, 124.7, 128.7, 132.7, 135.5, 142.5; HRMS (EI$^+$) calcd for $C_{16}H_{24}O$ 232.1827, found 232.1826.

***rac*-(*Z*)-3-(4a,8-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)but-2-enal (13).** A solution of alcohol **11** (0.026 g, 0.112 mmol) in CH_2Cl_2 (0.6 mL) was added to a stirred solution of Dess−Martin periodinane (0.071 g, 0.168 mmol) in CH_2Cl_2 (0.4 mL) over 2 min. After 5 min the homogeneous solution was diluted with 1.5 mL of ether, poured into saturated aqueous $NaHCO_3$ and water, and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (93:5:2 hexane/EtOAc/Et_3N) to afford 0.018 g (69%) of compound **13** as a yellow oil which, by NMR, showed a 1:88 *E*:*Z* (*E*-**13**:*Z*-**13**) ratio. FTIR (NaCl) ν 1670 (s) cm^{-1}; ^{1}H NMR (400.13 MHz, C_6D_6) δ 0.88 (s, 3H), 1.1−2.2 (m, 10H), 1.47 (s, 3H), 1.61 (d, J = 1.2 Hz, 3H), 6.01 (dq, J = 7.7, 1.2 Hz, 1H), 6.43 (s, 1H), 10.02 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100.63 MHz, C_6D_6) δ 18.8, 18.9, 23.1, 23.4, 24.8, 32.1, 33.3, 37.3, 38.0, 128.5, 130.1, 132.6, 132.7, 133.9, 163.0, 191.2; HRMS (EI$^+$) calcd for $C_{16}H_{22}O$ 230.1671, found 230.1673.

***rac*-(*E*)-3-(4a,8-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)but-2-enal (*E*-13).** A solution of iodine (0.002 g, 0.008 mmol) in hexane (0.1 mL) was added to a solution of aldehyde **13** (0.022 g, 0.095 mmol) in hexane (1.0 mL). After being stirred for 4 h, the solution was washed with a saturated

(29) (a) Domínguez, B.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **1998**, *63*, 4135−4139. (b) Alvarez, R.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron Lett.* **1998**, *39*, 5659−5662.

(30) Feliu, A. L.; Seltzer, S. *J. Org. Chem.* **1985**, *50*, 447−451.

aqueous $Na_2S_2O_3$ solution and the solvent was evaporated in vacuo, affording 0.020 g of a yellow solid (mp 62 °C, hexane/EtOAc) which by NMR showed a 7:1 *E*/*Z* (*E*-**13**:*Z*-**13**) isomer ratio (91%). FTIR (NaCl) ν 1662 (s) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.3−2.4 (m, 10H), 1.82 (s, 3H), 1.91 (s, 3H), 6.24 (d, J = 7.6 Hz, 1H), 6.88 (s, 1H), 10.18 (d, J = 7.6 Hz); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 13.8, 18.3, 19.0, 22.8, 23.2, 31.9, 33.4, 36.9, 37.4, 124.6, 128.2, 134.0, 134.1, 135.8, 156.8, 191.8; HRMS (EI^+): calcd for $C_{16}H_{22}O$ 230.1671, found 230.1670.

Ethyl *rac*-(2*E*,4*E*,6*Z*)-7-(4a,8-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)-3-methylocta-2,4,6-trienoate (16). A solution of diethyl 3-(ethoxycarbonyl)-2-methylprop-2-enylphosphonate **15** (0.122 g, 0.462 mmol) in THF (1.0 mL) was cooled to 0 °C and treated with DMPU (0.11 mL, 0.91 mmol) and *n*-BuLi (2.35 M in hexanes, 0.19 mL, 0.447 mmol). The mixture was stirred at this temperature for 20 min and then cooled to −78 °C. A solution of the aldehyde **13** (0.071 g, 0.308 mmol) in THF (1.0 mL) was slowly added, and the reaction mixture was stirred at −78 °C for 30 min. The mixture was allowed to warm to −40 °C to complete the reaction. Saturated aqueous NH_4Cl was added, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (95:5 hexane/EtOAc) to afford 0.073 g of **16** (70%) as a yellow oil. FTIR (NaCl) ν 1708 (s) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.0−2.5 (m, 10H), 1.28 (t, J = 7.1 Hz, 3H), 1.69 (s, 3H), 1.95 (s, 3H), 2.27 (d, J = 1.0 Hz, 3H), 4.16 (c, J = 7.1 Hz, 2H), 5.74 (s, 1H), 6.02 (d, J = 11.1 Hz, 1H), 6.21 (d, J = 15.3 Hz, 1H), 6.29 (s, 1H), 6.96 (dd, J = 15.3, 11.1 Hz, 1H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 13.8, 14.3, 18.5, 18.6, 23.2, 23.4, 25.0, 31.8, 33.0, 37.3, 37.8, 59.5, 117.8, 124.6, 126.0, 129.7, 132.8, 132.9, 133.2, 135.6, 146.2, 153.3, 167.3; HRMS (EI^+) calcd for $C_{23}H_{32}O_2$ 340.2402, found 340.2399.

***rac*-(2*E*,4*E*,6*Z*)-7-(4a,8-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)-3-methylocta-2,4,6-trienoic Acid (3).** A solution of ester **16** (0.015 g, 0.044 mmol) in ethanol (0.1 mL) was treated with 0.08 mL of 5 M aqueous KOH and refluxed for 30 min. The solution was cooled to room temperature, acidified with 10% HCl, and then extracted with a 70:30 Et_2O/CH_2Cl_2 mixture. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel (95:5 CH_2Cl_2/MeOH) to afford 0.01 g of **3** (77%) as a yellow solid (mp 198 °C, hexane/EtOAc). FTIR (NaCl): ν 3200−2900 (br), 1674 (s) cm^{-1}; ^1H NMR (400.13 MHz, CD_2Cl_2) δ 1.01 (s, 3H), 1.2−2.3 (m, 10H), 1.70 (s, 3H), 1.97 (s, 3H), 2.27 (d, J = 1.0 Hz, 3H), 5.77 (s, 1H), 6.04 (d, J = 10.6 Hz, 1H), 6.23 (d, J = 15.2 Hz, 1H), 6.29 (s, 1H), 7.02 (dd, J = 15.2, 10.6 Hz, 1H); ^{13}C NMR (100.63 MHz, CD_2Cl_2) δ 14.4, 18.8, 18.9, 23.3, 23.6, 25.4, 32.1, 33.3, 37.7, 38.2, 125.1, 126.2, 130.2, 133.1, 133.1, 133.3, 134.7, 136.0, 147.7, 156.3, 172.3; HMRS (EI^+) calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2082.

(*Z*)-3-(Cyclohex-1-en-1-yl)but-2-en-1-ol (27). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 mg, 0.087 mmol), triflate **20**[19c] (0.1 g, 0.434 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 0.25 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.053 g (80%) of **27** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.4−1.7 (m, 4H), 1.79 (s, 3H), 1.9−2.2 (m, 4H), 4.13 (d, J = 6.4 Hz, 2H), 5.3−5.4 (m, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 22.1, 22.7, 22.9, 25.0, 29.7, 60.3, 124.0, 124.5, 137.4, 143.0; HRMS (EI^+) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1197.

(*Z*)-3-(6-Methylcyclohex-1-en-1-yl)but-2-en-1-ol (28). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **21**[19a] (0.1 g, 0.410 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 1 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.052 mg (76%) of **28** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 1.4−1.8 (m, 4H), 1.79 (d, J = 1.0 Hz, 3H), 1.9−2.1 (m, 2H), 2.3−2.4 (m, 1H), 4.0−4.2 (m, 2H), 5.3−5.4 (m, 1H), 5.4−5.5 (m, 1H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 19.5, 20.1, 23.3, 25.4, 30.2, 31.1, 60.4, 124.4, 125.0, 142.1, 142.5; HRMS (EI^+) calcd for $C_{11}H_{18}O$ 166.1358, found 166.1352.

(*Z*)-3-(6,6-Dimethylcyclohex-1-en-1-yl)but-2-en-1-ol (29). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **22**[29a] (0.1 g, 0.387 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 5 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.058 g (84%) of **29** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.5−1.8 (m, 4H), 1.85 (d, J = 0.7 Hz, 3H), 2.02 (td, J = 6.3, 3.7 Hz, 2H), 4.02 (d, J = 6.9 Hz, 2H), 5.23 (t, J = 3.7 Hz, 1H), 5.45 (t, J = 6.9 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.4, 25.9, 26.8, 29.5, 34.1, 40.2, 61.4, 124.6, 126.6, 142.8, 145.9; HRMS (EI^+) calcd for $C_{12}H_{20}O$ 180.1514, found 180.1521.

(*Z*)-3-(2,6-Dimethylcyclohex-1-en-1-yl)but-2-en-1-ol (30). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **23**[19a] (0.1 g, 0.387 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 24 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 48 mg (70%) of **30** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3H), 1.3−1.8 (m, 4H), 1.50 (s, 3H), 1.73 (s, 3H), 1.9−2.0 (m, 2H), 2.2−2.3 (m, 2H), 3.96 (d, J = 7.2 Hz, 2H), 5.49 (t, J = 6.2 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.2, 20.4, 20.8, 23.0, 30.1, 31.5, 31.7, 61.5, 125.8, 128.2, 135.8, 139.4; HRMS (EI^+): calcd for $C_{12}H_{18}$ $[M - H_2O]^+$ 162.1409, found 162.1403.

(*Z*)-3-[(3*R*,6*S*)-6-Isopropyl-3-methylcyclohex-1-en-1-yl]-but-2-en-1-ol (31). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **24**[19d] (0.1 g, 0.349 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 24 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.062 g (85%) of **31** as a yellow oil. The NMR of the purified sample revealed the presence of an inseparable mixture of diastereomers in a 90:10 ratio, due to contamination of the starting ketone with its C-2 epimer. The major diastereomer showed the following spectroscopic data: ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.67 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.4−2.0 (m, 5H), 1.79 (s, 3H), 2.1−2.4 (m, 2H), 4.0−4.4 (m, 2H), 5.26 (d, J = 1.0 Hz, 1H), 5.3−5.5 (m, 1H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 16.9, 21.6, 21.7, 22.4, 23.8, 29.0, 31.1, 31.6, 42.0, 60.7, 125.4, 134.1, 140.7, 142.8. Selected spectroscopic data for the minor diastereomer: **(*Z*)-3-[(3*R*, 6*R*)-6-Isopropyl-3-methylcyclohex-1-en-1-yl]but-2-en-1-ol.** ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.74 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.4−2.0 (m, 5H), 1.79 (s, 3H), 2.1−2.4 (m, 2H), 4.0−4.4 (m, 2H), 5.26 (d, J = 1.0 Hz, 1H), 5.3−5.5 (m, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.6, 16.9, 18.1, 19.8, 22.0, 29.2, 29.7, 30.3, 40.8, 66.2, 125.7, 133.6, 140.3, 142.8.

(*Z*)-3-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-2-en-1-ol (32). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **25**[19a] (0.1 g, 0.368 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 72 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.04 g (56%) of **32** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.04 (s, 3H), 1.3−1.5 (m, 2H), 1.50 (s, 3H), 1.5−1.7 (m, 2H), 1.82 (d, J = 1.2 Hz, 3H), 1.97 (t, J = 6.4 Hz, 2H), 3.94 (d, J = 6.7 Hz, 2H), 5.5−5.6 (m, 1H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 19.5, 21.1, 26.1, 29.0, 30.6, 31.8, 34.5, 40.1, 61.9, 126.8, 127.7, 138.8, 139.6; HRMS (EI^+) calcd for $C_{13}H_{22}O$ 194.1671, found 194.1674.

6,6-Dimethyl-2-ethyl-1-[((trifluoromethyl)sulfonyl)oxy]-cyclohex-1-ene (26). A solution of di*iso*propylamine (0.20 mL, 1.426 mmol) in THF (2.0 mL) was cooled to 0 °C and treated

with *n*-BuLi (2.6 M in hexanes, 0.54 mL, 1.426 mmol). The mixture was stirred at this temperature for 30 min and then cooled to −78 °C. A solution of 2,2-dimethyl-6-ethyl-cyclohexanone[19e] (0.2 g, 1.296 mmol) in THF (2.0 mL) was slowly added, and the reaction mixture was stirred at −78 °C for an additional 2 h. A solution of *N*-phenyltrifluoromethanesulfonimide[31] (0.495 g, 1.387 mmol) in THF (2.0 mL) was then added, and the reaction mixture was allowed to slowly warm to room-temperature overnight. The solvent was removed in vacuo, aqueous 10% HCl was added, and the residue was then extracted with hexane. The combined organic layers were washed with 10% HCl, 10% NaOH, and water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, hexane), to afford 0.188 g of **26** as a pale yellowish oil (51%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.15 (s, 3H), 1.4−1.7 (m, 4H), 2.0−2.2 (m, 2H), 2.15 (q, J = 7.5 Hz, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 11.7, 18.5, 24.2, 26.5, 29.4, 35.6, 40.6, 118.7, 131.3, 149.5; HRMS (EI$^+$) calcd for $C_{11}H_{17}F_3O_3S$ 286.0851, found 286.0853.

(*Z*)-3-(2-Ethyl-6,6-dimethylcyclohex-1-en-1-yl)but-2-en-1-ol (33). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.01 g, 0.011 mmol), $AsPh_3$ (0.027 g, 0.087 mmol), triflate **26** (0.1 g, 0.367 mmol), and stannane **7** (0.17 g, 0.477 mmol) in NMP (1.2 mL) was stirred at 25 °C for 72 h. The residue was purified by chromatography (SiO_2, 85:15 hexane/EtOAc) to afford 0.03 g (41%) of **33** as a yellow oil. FTIR (NaCl): ν 3600−3100 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H), 0.93 (s, 3H), 1.04 (s, 3H), 1.4−1.8 (m, 4H), 1.83 (d, J = 1.2 Hz, 3H), 1.8−2.1 (m, 4H), 3.96 (d, J = 6.7 Hz, 2H), 5.50 (tq, J = 6.7, 1.2 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.3, 19.6, 26.8, 28.0, 28.5, 29.1, 30.8, 34.7, 40.3, 61.9, 126.7, 133.3, 138.2, 139.5; HRMS (EI$^+$) calcd for $C_{14}H_{24}O$ 208.1827, found 208.1836.

(*Z*)-3-(Tri-*n*-butylstannyl)but-2-enal (40). MnO_2 (14.4 g, 166 mmol) was added in one portion to a solution of alcohol **7** (2.0 g, 5.54 mmol) in CH_2Cl_2 (85 mL), and the mixture was stirred at 25 °C for 12 h. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (95:5 hexane/EtOAc) to afford 1.65 g (83%) of compound **40** as a yellow oil. FTIR (NaCl) ν 1686 (s) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 9H), 1.04 (t, J = 8.2 Hz, 6H), 1.31 (sextet, J = 7.3 Hz, 6H), 1.4−1.5 (m, 6H), 2.24 (d, J = 1.4 Hz, $^3J_{Sn-H}$ = 37.8 Hz, 3H), 6.69 (app dt, J = 7.0, 1.4 Hz, $^3J_{Sn-H}$ = 95.6 Hz, 1H), 9.47 (dd, J = 7.0, 1.0 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 10.9, 13.5, 27.2, 28.5, 28.9, 141.4, 179.0, 193.5; HRMS (FAB$^+$) calcd for $C_{12}H_{13}O^{116}Sn$ 299.0766, found 299.0757.

(*E*)-3-(Tri-*n*-butylstannyl)but-2-enal (43). MnO_2 (3.9 g, 45 mmol) and Na_2CO_3 (4.8 g, 45 mmol) were added to a solution of alcohol **18** (0.9 g, 2.5 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred at 25 °C for 16 h and then filtered through Celite. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (94:5:1 hexane/EtOAc/Et_3N) to afford 0.76 g of **43** (85%) as a yellow oil. FTIR (NaCl) ν 1678 (s) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.90 (m, 9H), 1.00 (t, 6H, J = 8.2 Hz), 1.2−1.4 (m, 6H), 1.4−1.6 (m, 6H), 2.46 (d, J = 1.8 Hz, $^3J_{Sn-H}$ = 43.4 Hz, 3H), 6.22 (dq, J = 8.0, 1.7 Hz, $^3J_{Sn-H}$ = 59.9 Hz, 1H), 10.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 9.3, 13.5, 20.6, 27.2, 28.9, 139.8, 174.1, 187.3; HRMS (FAB$^+$) calcd for $C_{12}H_{23}O^{120}Sn$ 303.0771, found 303.0757.

(*E*)-4-(Tri-*n*-butylstannyl)pent-3-en-2-ol (44). A solution of aldehyde **43** (0.76 g, 2.1 mmol) in THF (20 mL) at −78 °C was treated with MeLi (1.6 M in hexanes, 1.4 mL, 2.2 mmol) and stirred at this temperature for 15 min. After standard workup, the residue was purified by chromatography on silica gel (80:20 hexane/EtOAc) to afford 0.64 g (81%) of **44** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 15H), 1.23 (d, J = 6.3 Hz, 3H), 1.30 (sextet, J = 7.3 Hz, 6H), 1.4−1.6 (m, 6H), 1.89 (d, J = 1.5 Hz, $^3J_{Sn-H}$ = 45.5 Hz, 3H), 4.7−4.8 (m, 1H), 5.57 (d, J = 7.8 Hz, $^3J_{Sn-H}$ = 68.5 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 9.0, 13.7, 19.4, 23.3, 27.3, 29.1, 63.5, 140.3, 144.5; HRMS (EI$^+$) calcd for $C_{17}H_{35}O^{118}Sn$ 373.1704, found 373.1698.

5-(Tri-*n*-butylstannyl)hex-5-en-1-ol (38c). *n*-BuLi (2.3 M in hexane, 4.8 mL, 11 mmol) was slowly added to a solution of hexa-*n*-butylditin (6.4 g, 11 mmol) in THF (25 mL) at −30 °C, and the reaction mixture was stirred at that temperature for 1 h. CuCN (0.49 g, 5.5 mmol) was added in one portion and after being stirred for 1 h at −30 °C, the temperature was lowered to −78 °C and a solution of compound **36c** (0.5 g, 5 mmol) in THF (4 mL) was added. The reaction was stirred for 1 h at −78 °C, and it was quenched by addition of MeOH (12 mL). After being stirred for 1 h, a mixture of saturated aqueous NH_4Cl solution and NH_4OH (90:10 v/v) was added, and the temperature was raised to 25 °C. The mixture was extracted with Et_2O, and the combined organic extracts were washed with NH_4Cl, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (89:10:1 hexane/EtOAc/Et_3N) to afford 1.2 g (62%) of **38c** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 15H), 1.31 (sextet, J = 6.4 Hz, 6H), 1.4−1.6 (m, 10H), 2.27 (t, J = 7.5 Hz, $^3J_{Sn-H}$ = 46.3 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 5.12 (d, J = 2.6 Hz, $^3J_{Sn-H}$ = 63.7 Hz, 1H), 5.68 (d, J = 2.6 Hz, $^3J_{Sn-H}$ = 139.6 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 9.5, 14.7, 25.5, 27.3, 29.1, 32.4, 40.9, 62.8, 125.0, 155.1; HRMS (FAB$^+$) calcd for $C_{14}H_{29}O^{116}Sn$ 329.1236, found 329.1234.

***tert*-Butyldimethylsilyl 3-(Tri-*n*-butylstannyl)but-3-en-1-yl Ether (39).** Imidazole (0.15 g, 2.2 mmol) and *tert*-butyldimethylsilyl chloride (0.17 g, 1.13 mmol) were added to a solution of **38a** (0.36 g, 0.93 mmol) in DMF (5 mL). After stirring at 25 °C for 1 h, H_2O (10 mL) was added, and the mixture was extracted with hexane. The combined organic extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (hexane) to afford 0.43 g (92%) of **39** as a colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (t, J = 7.4 Hz, 15H), 0.90 (s, 9H), 1.31 (sextet, J = 7.4 Hz, 6H), 1.4−1.5 (m, 6H), 2.48 (t, J = 7.6 Hz, $^3J_{Sn-H}$ = 46.5 Hz, 2H), 3.62 (t, J = 7.6 Hz, 2H), 5.18 (d, J = 2.8 Hz, $^3J_{Sn-H}$ = 61.8 Hz, 1H), 5.74 (dd, J = 2.8, 1.4 Hz, $^3J_{Sn-H}$ = 137.4 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ -5.2, 9.5, 13.7, 18.5, 26.0, 27.4, 29.1, 44.6, 63.4, 127.2, 150.9; HRMS (FAB$^+$) calcd for $C_{18}H_{39}OSi^{116}Sn$ 415.1788, found 415.1784.

(*E*)-4-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-3-en-1-ol (45). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.0057 g, 0.006 mmol), $AsPh_3$ (0.015 mg, 0.05 mmol), triflate **25** (0.068 g, 0.25 mmol), and stannane **37** (0.097 g, 0.27 mmol) in NMP (3.5 mL) was stirred at 50 °C for 5 h. The residue was purified by chromatography (SiO_2, 90:10 hexane/EtOAc) to afford 30 mg (62%) of **45** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.98 (s, 6H), 1.4−1.6 (m, 4H), 1.66 (d, J = 0.8 Hz, 3H), 1.96 (t, J = 6.1 Hz, 2H), 2.38 (app qd, J = 6.9, 1.1 Hz, 2H), 3.6−3.7 (m, 2H), 5.34 (dt, J = 15.8, 6.9 Hz, 1H), 5.96 (dd, J = 15.8, 0.8 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 19.2, 21.5, 28.7, 32.6, 33.7, 36.6, 39.2, 62.1, 128.3, 129.6, 131.0, 137.3; HRMS (EI$^+$) calcd for $C_{13}H_{22}O$ 194.1671, found 194.1678.

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)-penta-2,4-dien-1-ol (46). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.006 g, 0.006 mmol), $AsPh_3$ (0.015 g, 0.05 mmol), triflate **25** (0.068 g, 0.25 mmol), and stannane **35** (0.104 g, 0.27 mmol) in NMP (3 mL) was stirred at 50 °C for 5 h. The residue was purified by chromatography (SiO_2, 90:10 hexane/EtOAc) to afford 25 mg (45%) of **46** as a yellow oil. FTIR (NaCl) ν 3319 (br) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.4−1.7 (m, 4H), 1.69 (d, J = 0.7 Hz, 3H), 1.85 (s, 3H), 2.00 (t, J = 5.7 Hz, 2H), 4.30 (d, J = 7.0 Hz, 2H), 5.62 (t, J = 7.0 Hz, 1H), 6.03 (d, J = 16.2 Hz, 1H), 6.13 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 12.7, 19.5, 21.9, 29.1, 33.1, 34.4, 39.7, 59.7, 127.4, 128.6,

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129.2, 137.2, 137.3, 137.8; HRMS (EI^+) calcd for $C_{15}H_{24}O$ 220.1827, found 220.1826.

(*Z*)-4-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-3-en-2-ol (48). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.047 g, 0.051 mmol), $AsPh_3$ (0.126 g, 0.41 mmol), triflate **25** (0.558 g, 2.05 mmol), and stannane **41** (0.846 g, 2.25 mmol) in NMP (27 mL) was stirred at 60 °C for 16 h. The residue was purified by chromatography (SiO_2, 90:10 hexane/EtOAc) to afford 0.274 g (64%) of **48** as a yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.06 (s, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.4−1.5 (m, 2H), 1.47 (s, 3H), 1.6−1.7 (m, 2H), 1.79 (d, J = 1.3 Hz, 3H), 1.97 (t, J = 6.5 Hz, 2H), 4.1−4.2 (m, 1H), 5.30 (dq, J = 8.4, 1.3 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 19.1, 21.0, 22.9, 25.7, 28.9, 30.3, 31.4, 33.7, 39.8, 66.2, 127.8, 131.5, 137.2, 138.4; HRMS (EI^+) calcd for $C_{14}H_{24}O$ 208.1827, found 208.1822.

3-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-3-en-1-ol (49). According to the general procedure described above, a mixture of $Pd_2(dba)_3$ (0.006 g, 0.006 mmol), $AsPh_3$ (0.015 g, 0.05 mmol), triflate **25** (0.068 g, 0.25 mmol), and stannane **38a** (0.097 g, 0.27 mmol) in NMP (3.5 mL) was stirred at 50 °C for 16 h. The residue was purified by chromatography (SiO_2, 90:10, hexane/AcOEt) to afford 0.02 g (20%) of starting material **38a** and 0.025 g (51%) of **49** as a yellow oil. FTIR (NaCl) ν 3600−3100 (br) cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.4−1.5 (m, 2H), 1.56 (s, 3H), 1.6−1.7 (m, 2H), 1.9−2.0 (m, 2H), 2.3−2.4 (m, 2H), 3.82 (t, J = 6.4 Hz, 2H), 4.68 (d, J = 1.0 Hz, 1H), 5.05 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 19.1, 21.1, 28.6, 29.6, 31.7, 33.9, 39.7, 40.5, 60.8, 113.7, 127.2, 141.2, 145.7; HRMS (EI^+) calcd for $C_{13}H_{22}O$ 194.1671, found 194.1668.

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Supporting Information Available: Experimental procedures for the synthesis of compound **4**, and copies of ^1H and ^{13}C NMR spectra for compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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