Tetrahedron 66 (2010) 4775–4783

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The regio- and stereochemical course of reductive cross-coupling reactions between 1,3-disubstituted allenes and vinylsilanes: synthesis of (*Z*)-dienes

Allan U. Barlan, Glenn C. Micalizio *

Department of Chemistry, The Scripps Research Institute, Scripps Florida, Jupiter, FL 33458, USA

ARTICLE INFO

Article history:
Received 13 January 2010
Received in revised form 12 February 2010
Accepted 16 February 2010
Available online 21 February 2010

Keywords:
Allenes
Titanium
Reductive Cross-Coupling
Z-dienes

ABSTRACT

In investigations aimed at exploring the potential of disubstituted allenes in stereoselective synthesis, we report studies that explore the reductive cross-coupling reaction of vinylsilanes with a range of substituted allenes. Regiochemical control is attained by employing allenic alkoxides, where the proximal heteroatom dictates the site-selectivity in a process that proceeds by net formal metallo-[3,3] rearrangement (directed carbometalation/elimination). Stereoselectivity in these reactions is complex, with both the nature of allene substitution and relative stereochemistry of the substrate impacting the stereoselective generation of each alkene of a substituted 1,3-diene.

1. Introduction

Reductive cross-coupling is emerging as a useful strategy for bimolecular C–C bond formation.[1] While a great many reports continue to appear for the coupling of substituted alkynes with carbonyl-based reaction partners,[2] studies that describe the related bimolecular union of coupling partners that diverge from these well-studied processes are rare.[3] In a program aimed at the elucidation of reductive cross-coupling reactions between alkynes, allenes, and alkenes, we have put forth a variety of heteroatom-directed reaction designs to accomplish selective cross-coupling.[4] These designs, which vary by the sequence of steps that result in encapsulation of the metal during the metal-centered [2+2+1] process, have proven to be useful for: (1) control of hetero- vs homo-coupling, (2) control of regioselectivity, (3) control of relative stereochemistry, and in some cases, (4) provide a means of overcoming the typical sluggish reactivity of highly substituted substrates in reductive cross-coupling chemistry (Fig. 1).[5]

In the course of a recent campaign in total synthesis, we experienced a great deal of difficulty associated with the efficient preparation of a trisubstituted (*Z*,*E*)-1,3-diene (Fig. 2).[6] While we were able to forge the C7–C8 sigma bond of callystatin A by application of well-known palladium-catalyzed coupling chemistry,[7] the synthesis of the stereodefined trisubstituted vinyliodide **1** was quite challenging. Initial explorations relied on multistep

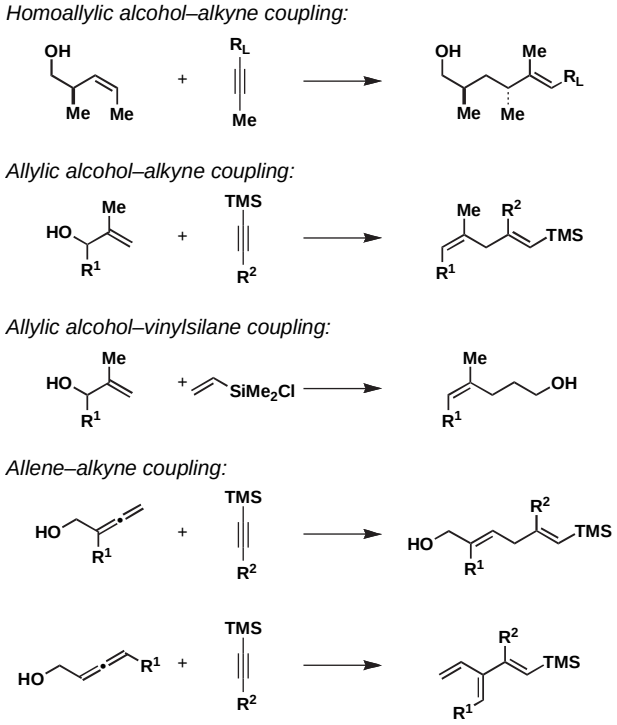


Figure 1. Recent examples of heteroatom-directed reductive cross-coupling reactions of alkynes and alkenes.

* Corresponding author. E-mail address: glenn.micalizio@yale.edu (G.C. Micalizio).

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.02.062

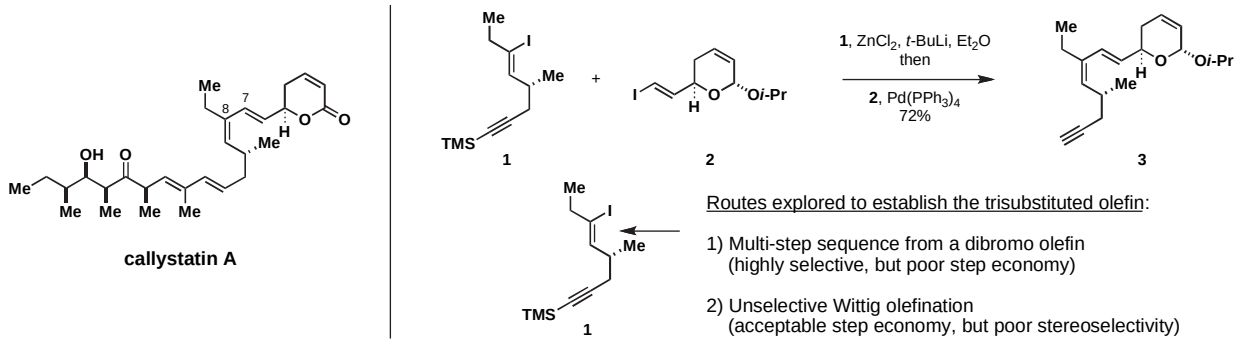


Figure 2. Difficulties experienced in establishing the C6–C9-(*Z*,*E*)-diene of callystatin A.

functionalization of a dibromo-olefin that proceeded through conversion to a TMS-alkyne, hydrozirconation, iodination, and Pd-catalyzed ethylation.[8] In an effort to increase step-economy for the synthesis of **1**, we ultimately pursued Wittig chemistry between an α-chrial aldehyde and an iodoethyl-substituted ylid. While this revised route provided a concise entry to the desired vinyliodide, stereoselectivity for the Wittig olefination was 1.7:1, favoring the formation of the *undesired isomer*.[6,9] Fortunately, chromatographic separation of these isomers was possible and a total synthesis of callystatin A was accomplished in 11 steps from a commercially available chiral alcohol.

The difficulty in establishing the C6–C9 1,3-(*Z*,*E*)-diene in callystatin prompted us to develop an alternative pathway to establish this type of stereodefined motif. Previous studies in our laboratory had revealed that alkoxide-directed reductive cross-coupling of disubstituted allenes with internal alkynes defined a regio- and stereoselective pathway to cross-conjugated trienes (**4**+**5**→**6**; Fig. 3).[4i] We speculated that a related reductive cross-coupling reaction between substituted allenes and terminal alkenes could provide a useful pathway to trisubstituted (*Z*,*E*)-dienes (**7**+**8**→**9**) of the substitution pattern seen in C6–C9 of callystatin A. Here, we discuss our studies of this proposed process, and present the scope and limitations of a stereoselective reductive cross-coupling reaction between disubstituted allenes and vinylsilanes for the synthesis of (*Z*)-olefin-containing 1,3-dienes.

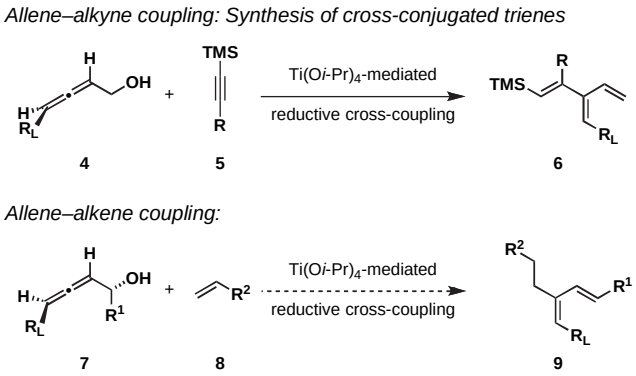
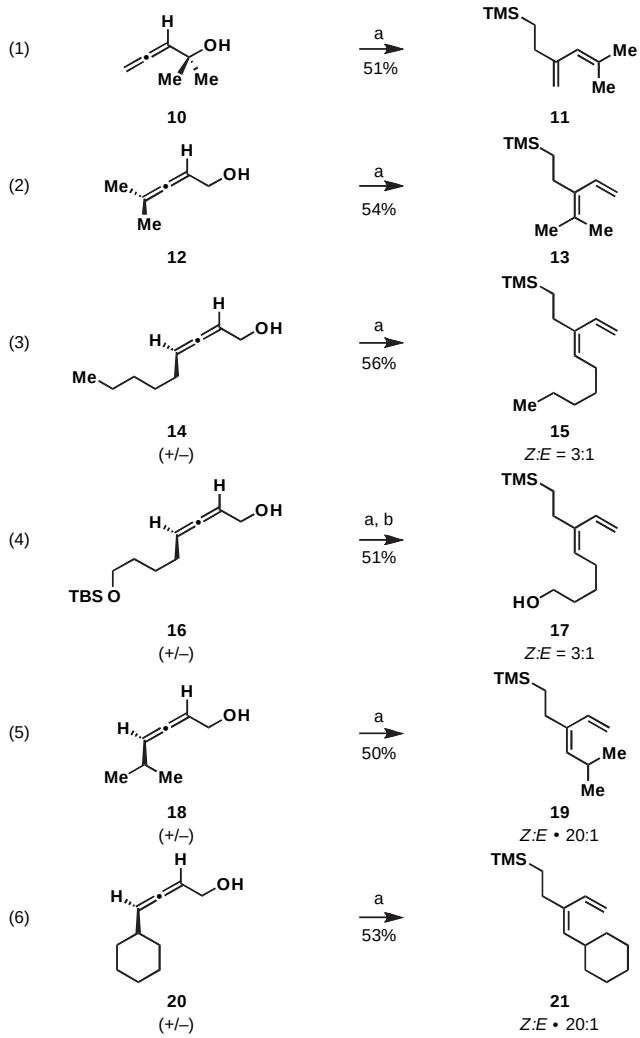


Figure 3. Allene–alkene reductive cross-coupling for the synthesis of *Z*-dienes.

2. Results and discussion

Exploring the utility of a reaction design based on stepwise encapsulation of the metal center in a reductive cross-coupling reaction of allenes with alkenes, we initiated studies of this process with vinyltrimethylsilane—a simple monosubstituted alkene, that is, well known to be a substrate for Ti(IV) alkoxide-mediated coupling reactions.[10] As illustrated in Eqs. 1 and 2 of Figure 4, the basic bond construction proved feasible. Reaction of the isomeric allenic alcohols **10** and **12** with a preformed Ti-complex of vinyltrimethylsilane resulted in formation of the stereo-undefined



Reaction conditions: a) vinyltrimethylsilane, Ti(O*i*-Pr)$_4$, *c*-C_5H_9MgCl, Et_2O (–78 to –50 °C), then add lithium alkoxide of the allenyl alcohol. b) TBAF, THF.

Stereochemical assignment of the (*Z*)-diene products was accomplished by nOe analysis. For example:

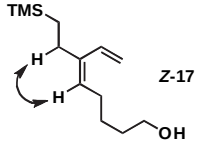


Figure 4. Exploring the basic bond construction: reductive crosscoupling between substituted allenes and vinyltrimethylsilane.

trisubstituted 1,3-dienes **11** and **13** in 51 and 53% yield. In addition to validating the proposed coupling process, Eq. 2 demonstrated that this allene–alkene union is effective for establishing a tetrasubstituted alkene.

Next, in a brief study, the structural requirements for (*Z*)-selectivity were examined. Reductive cross-coupling of disubstituted allenes that contain an unbranched substituent distal to the hydroxymethyl group (**14** and **16**; Eqs. 3 and 4) proved to be relatively poor substrates for this process. While these coupling reactions proceeded with acceptable conversions (51–56% yield), the resulting dienes (**15** and **17**) were formed with only moderate levels of selectivity (*Z*:*E*=3:1). In accord with previous observations made in our study of allene–imine[4k] and allene–alkyne[4h,i] reductive cross-coupling reactions, (*Z*)-selectivity is markedly enhanced with substrates that contain branched alkyl substituents distal to the hydroxymethyl group. As illustrated in Eqs. 5 and 6, the isopropyl- and cyclohexyl-substituted allenes **18** and **20** were converted to the dienes **19** and **21** in 50 and 53% yield, each with ≥20:1 selectivity for the formation of the (*Z*)-diene product.

While we were pleased with the success of our initial investigation, we recognized that the tetraalkylsilane products derived from this coupling process are of limited general synthetic utility. As such, we briefly explored the potential of employing this (*Z*)-selective coupling reaction for the union of allenes with other coupling partners. Coupling of allene **16** with styrene was successful, but led to the production of the (*Z*)-diene **23** in 52% yield (Fig. 5).[11] As would be anticipated from our earlier investigation of allene **16**, this coupling reaction proceeded with low levels of stereoselectivity (*Z*:*E*=2:1). Unfortunately, all attempts to accomplish this reductive cross-coupling with simple terminal alkenes was met with failure; in all cases resulting in the formation of complex product mixtures.

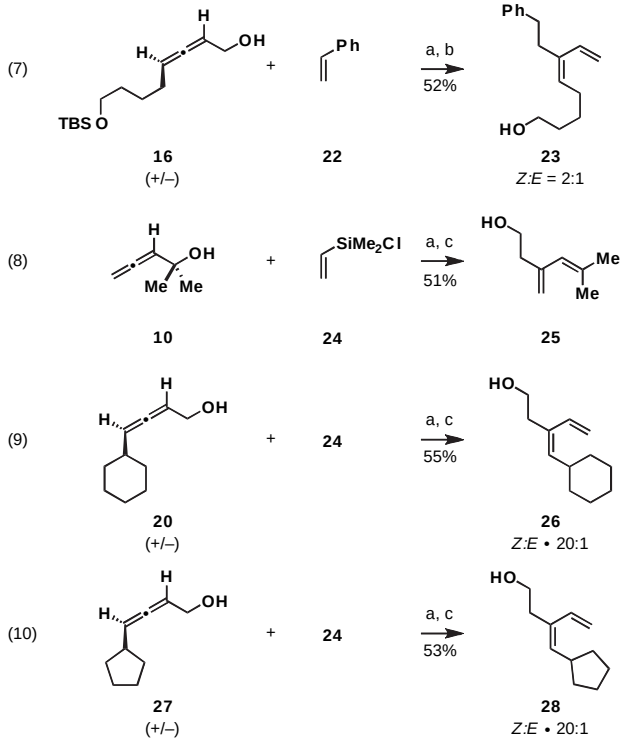
Inspired by the Kulinkovich reaction,[12] we hoped that we could employ EtMgBr as a coupling partner in this (*Z*)-diene-forming coupling reaction. Based on the presumed mechanistic course of the Kulinkovich reaction, that is, thought to proceed by the conversion of EtMgBr to a Ti–ethylene complex,[12b] coupling with allenyl alcohols should result in a net stereoselective ethylation.[13] Such a process would define a direct approach to the synthesis of the (*Z*,*E*)-diene of callystatin A. Unfortunately, all attempts to accomplish this transformation were also unsuccessful and led to the formation of complex product mixtures.[14]

Moving on, we refocused our attention on an inexpensive and readily available vinylsilane that, when coupled to substituted allenes would provide a product that could be easily functionalized. This concept was validated as described in Eq. 8 (Fig. 5). Here, coupling of the tertiary alcohol **10** with vinyldimethylchlorosilane **24**, followed by oxidation of the σ_{C-Si}, provided the primary carbinol **25** in 51% yield (over two steps). Illustrated in Eqs. 9 and 10, a two-step process of reductive cross-coupling and oxidation delivered the stereodefined (*Z*)-diene-containing primary alcohols **26** and **28** from the racemic allenes **20** and **27**. In each case, the (*Z*)-diene product was formed with ≥20:1 stereoelectivity.

Returning to our initial problem, defined by the goal of designing a reductive cross-coupling reaction for the establishment of each stereodefined alkene of a (*Z*,*E*)-diene, we questioned whether the present allene–vinylsilane coupling reaction proceeds in a stereospecific fashion (Fig. 6). If ligand exchange is a prerequisite for carbometalation (**A**→**B**→**C**) in this reductive cross-coupling reaction, the conversion of preformed metallacyclopropanes (**A**) to 1,3-diene products was anticipated to follow from a precise sequence of steps whereby the (*Z*)-trisubstituted alkene would derive from stereoselective carbometalation *anti* to R^2 (**B**→**C**), and the (*E*)-disubstituted alkene would result from stereospecific elimination (**C**→**D**).

In an effort to explore this proposal, two stereodefined allenes were prepared as described in Figure 7. The isomerically pure diols **29** and **31** were accessed from *syn*-dihydroxylation of the corresponding (*Z*)- and (*E*)-enynes, each prepared from Sonogashira coupling with TMS–acetylene.[15] Stereoselective conversion to the isomerically defined allenes **30** and **32** followed from a two-step sequence composed of carbonate formation and S_N2' addition.[16]

The coupling of allenes **30** and **32** with vinyldimethylchlorosilane is depicted in Figure 8. These reactions, performed as previously discussed in Figure 5, provided substituted 1,3-dienes **33** and **34** with varying levels of selectivity. While in each case, the (*Z*)-trisubstituted alkene of the products was established with high levels



Reaction conditions: a) alkene, Ti(O*i*-Pr)$_4$, *c*-C_5H_9MgCl, Et_2O (–78 to –50 °C), then add lithium alkoxide of the allenyl alcohol. b) TBAF, THF, c) KF, $KHCO_3$, H_2O_2, MeOH, THF.

Figure 5. Reductive cross-coupling reactions of allenyl alcohols with styrene and chlorodimethylvinylsilane.

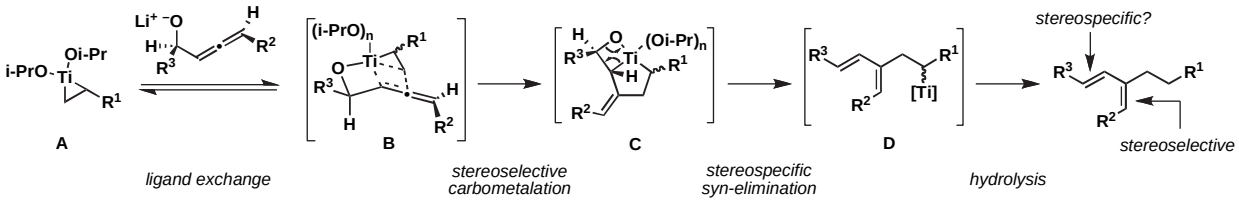
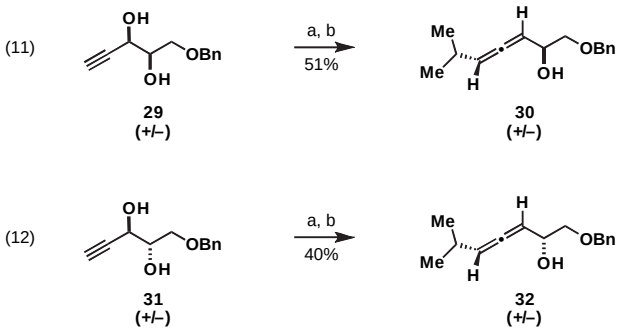


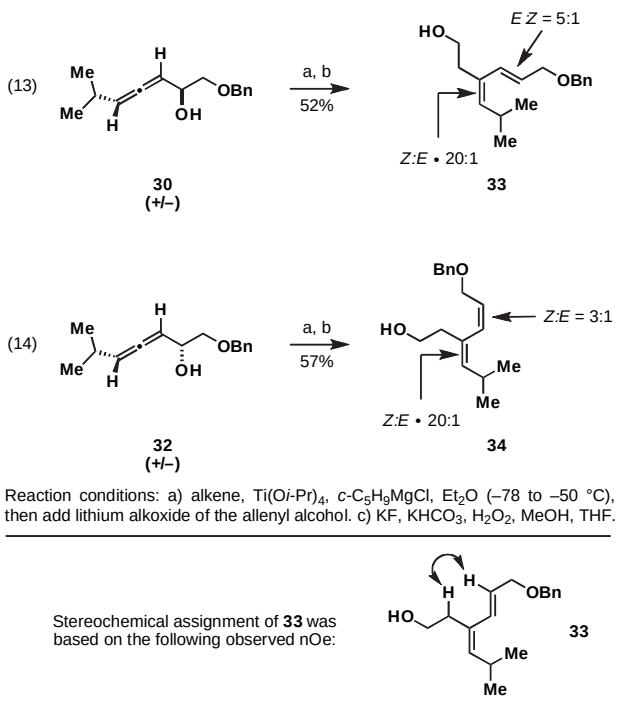
Figure 6. Allene–alkene reductive cross-coupling for the synthesis of (*Z*)-dienes.



Reaction conditions: a) CDI, PhH, reflux. b) *i*-PrMgCl, $CuBr{\bullet}SMe_2$.

Figure 7. Preparation of isomeric allenes.

of selectivity (Z:$E \geq 20$:1), the disubstituted alkenes of these products was accessed with only moderate levels of selectivity (E:Z=5:1 and 1:3). This observation is consistent with a mechanistic picture composed of: (1) stereoselective *syn*-carbometalation, and (2) competition between *syn*- and *anti*-elimination of the organometallic intermediate.



Reaction conditions: a) alkene, $Ti(O\textit{i}\text{-}Pr)_4$, *c*-$C_5H_9MgCl$, Et_2O (–78 to –50 °C), then add lithium alkoxide of the allenyl alcohol. c) KF, $KHCO_3$, H_2O_2, MeOH, THF.

Stereochemical assignment of **33** was based on the following observed nOe:

Figure 8. Stereoselective access to (*Z*,*E*)- and (*Z*,*Z*)-1,3-dienes by reductive cross-coupling.

If ligand exchange was a prerequisite to C–C bond formation, we would expect that the coupling reaction between allene **30** and vinyldimethylchlorosilane would deliver the (*Z*,*E*)-1,3-diene **33** with very high levels of stereochemical purity. This expectation follows from a rationale based on facile *syn*-elimination of the resulting bicyclic metallacyclopentane (**C**; Fig. 8) in preference to ring opening and *anti*-elimination to deliver the (*Z*)-disubstituted alkene product.[17] The appreciable quantity of (*Z*,*Z*)-diene observed (17% of the 1,3-diene product isolated) is consistent with *anti*-elimination by way of a stereodefined monocyclic metallacyclopentane—itself, likely derived from a competing reaction pathway that does not proceed through alkoxide-directed carbometalation. While such stereochemical erosion has not been observed in related coupling reactions of substituted allylic alcohols,[4j,4l–p] the current observation may relate to the increased reactivity of allenes in bimolecular metal-mediated reductive cross-coupling.[18] Overall, this enhanced reactivity (and associated competing non-directed carbometalation) may represent an inherent limitation to the use of allenic alkoxides in stereoselective reductive cross-coupling chemistry. That said, the examples described here demonstrate the potential to employ reductive cross-coupling for the stereoselective synthesis of (*Z*,*E*)- and (*Z*,*Z*)-trisubstituted 1,3-dienes from isomerically pure disubstituted allenyl alcohols.

3. Conclusion

While reductive cross-coupling chemistry is well known for the union of alkynes with polarized π-bonds (carbonyl electrophiles), it is only beginning to emerge as a useful strategy for union of more substituted and electronically unactivated π-systems (i.e., alkenes, alkynes, and allenes). In efforts directed at the application of an alkyne–alkyne reductive cross-coupling reaction in natural product synthesis, we identified a significant challenge in the establishment of the C6–C9 (*Z*,*E*)-1,3-diene of callystatin A. Here, we describe the design and investigation of a new allene–alkene reductive cross-coupling to address this problem in stereoselective synthesis. Our results lead us to conclude that the present coupling reaction provides a highly stereoselective route to the generation of 1,3-dienes that contain a (*Z*)-trisubstituted alkene. While our data reveals that this coupling process does not proceed in a stereospecific fashion, we have discovered a reductive cross-coupling reaction that forges a central C–C bond in concert with the establishment of two stereodefined alkenes.

4. Experimental section

4.1. General experimental information

All reactions were conducted in flame-dried glassware under nitrogen or argon using anhydrous solvents. Toluene, tetrahydrofuran, and diethyl ether were used after passing through an activated alumina column. $Ti(O\textit{i}\text{-}Pr)_4$ was used after distillation of the commercially available reagent. All other commercially available reagents were used as received (Aldrich). ^1H NMR data were recorded at 400 MHz on a Bruker AM-400 in $CDCl_3$. ^{13}C NMR data were recorded at 100 MHz on a Bruker AM-400. Infrared spectra were recorded on a PerkinElmer SpectrumOne FTIR instrument. Low resolution mass spectra were acquired on a Varian 500-MS mass spectrometer under soft ionization mode. HRMS data (ESI-TOF-MS) were obtained by the University of Florida Mass Spectrometry lab. ^1H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.16 ppm). Chromatographic purification was performed using 60 Å, 35–75 μ particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Semi-preparative HPLC normal phase separations were performed using an HPLC system composed of two Dynamax SD-1 pumps, a Rheodyne injector, and a Dynamax UV-1 absorbance detector.

4.2. Cross-coupling between substituted allenes and vinyltrimethylsilane

*4.2.1. General synthesis of diene **6**.* To a −78 °C solution of alkene **5** (1.1 equiv) in diethyl ether (0.1 M) was added $ClTi(O\textit{i}\text{-}Pr)_3$ (1.1 equiv) and *c*-C_5H_9MgCl (2.2 equiv) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C

solution of allene **4** (1 equiv) in THF (0.5 M) was added *n*-BuLi (1.1 equiv) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (ethyl acetate/hexanes) to yield diene **6** as a clear oil.

*4.2.2. 1-Trimethylsilyl-3-methylene-5-methyl-hex-4-ene (**11**).* To a −78 °C solution of vinyltrimethylsilane (0.161 mL, 1.1 mmol) in 11 mL of diethyl ether (0.1 M) was added 1.1 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 1.1 mmol) and 1.1 mL of *c*-C_5H_9MgCl (2.00 M in ether, 2 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **10** (0.119 mL, 1 mmol) in 2 mL THF was added 0.440 mL of *n*-BuLi (2.54 M in hexanes, 1.1 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (hexanes) to yield diene **11** as a clear oil (93 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.97 (d, *J*=4.8 Hz, 1H), 4.72 (d, 1H), 2.06–2.02 (m, 2H), 1.80 (s, 3H), 1.79 (s, 3H), 0.65–0.60 (m, 2H), 0.001 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 134.9, 126.3, 111.0, 31.9, 26.8, 19.7, 15.5, −1.6; IR (thin film, NaCl) 3443, 2953, 1731, 1377, 1248, 1178, 1064, 838, 758, 691 cm^{-1}; HRMS (EI, M^+) calcd for $C_{11}H_{22}Si$, 182.1491 *m*/*z* (M); observed 183.1560 $(M+H)^+$ *m*/*z*.

*4.2.3. 1-Trimethylsilyl-4-methyl-3-vinyl-pent-3-ene (**13**).* To a −78 °C solution of vinyltrimethylsilane (0.352 mL, 2.4 mmol) in 24 mL of diethyl ether (0.1 M) was added 2.4 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 2.4 mmol) and 2.4 mL of *c*-C_5H_9MgCl (2.00 M in ether, 4.8 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **12** (0.235 g, 2 mmol) in 2 mL of THF was added 0.880 mL of *n*-BuLi (2.50 M in hexanes, 2.2 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (hexanes) to yield diene **13** as a clear oil (196.5 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J*=11.0, 17.4 Hz, 1H), 5.06 (d, *J*=17.4 Hz, 1H), 4.96 (d, *J*=11.0 Hz, 1H), 2.22–2.18 (m, 2H),1.80 (s, 3H), 1.77 (s, 3H), 0.62–0.58 (m, 2H) 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 134.4, 130.3, 110.1, 22.8, 21.8, 21.3, 16.5, −1.7; IR (thin film, NaCl) 3444, 2954, 1731, 1464, 1383, 1248, 861, 757, 691, 466 cm^{-1}; HRMS (EI, M^+) calcd for $C_{11}H_{22}Si$, 182.1491 *m*/*z* (M); observed 183.1566 $(M+H)^+$ *m*/*z*.

*4.2.4. (Z)-1-Trimethylsilyl-3-vinyl-non-3-ene (**15**).* To a −78 °C solution of vinyltrimethylsilane (0.190 mL, 1.3 mmol) in 15 mL of diethyl ether (0.1 M) was added 1.3 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 1.3 mmol) and 1.3 mL of *c*-C_5H_9MgCl (2.00 M in ether, 2.6 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **14** (0.165 g, 1.17 mmol) in 2 mL THF was added 0.518 mL of *n*-BuLi (2.50 M in hexanes, 1.3 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* selectivity was determined by ^{1}H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (hexanes) to yield diene **15** as a clear oil (147.3 mg, 56%, *Z*:*E* 3:1). The stereochemistry of the major product was assigned by analogy to previous examples. (peaks correlating to the major *Z*-isomer were extracted from the spectrum of the 3:1 mixture) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, *J*=10.8, 17.2 Hz, 1H), 5.43–5.37 (m, 1H), 5.17 (d, *J*=17.6 Hz, 1H), 5.06 (d, *J*=17.6 Hz, 1H), 2.20–2.12 (m, 2H+2H), 1.37–1.27 (m, 2H+2H+2H), 0.89 (t, 3H), 0.70 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (**15** ***Z***+***E***) (100 MHz, $CDCl_3$) δ 141.4, 140.2, 138.9, 133.0, 132.3, 129.8, 112.8, 110.1, 31.8, 29.8, 29.5, 28.1, 27.5, 22.8, 22.7, 16.8, 16.1, 14.3, −1.6, −1.8; IR (thin film, NaCl) 3444, 2954, 2860, 1755, 1714, 1463, 1248, 837, 757, 692 cm^{-1}; HRMS (EI, M^+) calcd for $C_{14}H_{28}Si$, 224.1960 *m*/*z* (M); observed 225.2028 $(M+H)^+$ *m*/*z*.

*4.2.5. Synthesis of allene **16**.* To a mixture of *n*-BuLi (2.51 M in hexanes, 1.1 equiv) in THF (0.16 M) was added dropwise tetrahydro-2(2-propynyloxy)-*2H*-2-pyran (1 equiv) at −78 °C under Ar. After the mixture was stirred for 1 h, 5-(*tert*-butyldimethylsiloxy)-pentanal (1.11 equiv) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C, warmed to room temperature, stirred for 24 h, and added 20 mL of satd aq NH_4Cl. The mixture was extracted with 3×50 mL EtOAc, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography on silica gel (10–15% ethyl acetate/hexanes) to yield alcohol of **16** as a clear oil. (1.451 g, 61%). To a solution of triphenylphosphine (1.3 equiv) in THF (0.16 M) in a flame-dried round bottom flask at −15 °C under Ar was added diethyl azodicarboxylate (1.3 equiv) and stirred for 10 min. To the above solution was then added alcohol (1 equiv) and stirred for 10 min. Then *o*-nitrobenzenesulfonylhydrazine (1.3 equiv) was added, stirred for 1 h at −15 °C, warmed to room temperature, and stirred for 17 h. Subsequently, the solution was concentrated in vacuo and was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to yield THP-protected allene of **16** as a clear oil (1.407 g, 62%). To a solution of THP-protected allene of **16** (1 equiv) in Et_2O (0.1 M) was added $MgBr_2$–Et_2O (3 equiv). The resulting solution was stirred at room temperature for 17 h and then added 10 mL of Et_2O. The resulting mixture was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to yield allene **16** as a clear oil (0.424 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34–5.29 (m, 1H+1H), 4.13–4.09 (m, 2H), 3.64–3.60 (m, 2H), 2.07–2.03 (m, 2H), 1.60–1.58 (m, 2H), 1.57–1.49 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 93.9, 92.2, 63.2, 61.0, 32.2, 28.4, 26.1, 25.4, 18.5, −5.1; IR (thin film, NaCl) 3380, 2857, 1964, 1727, 1655, 1471, 1360, 1255, 1105, 1024, 836, 775, 663, 565 cm^{-1}; LRMS (EI, M^+) calcd for $C_{14}H_{28}O_2Si$, 256.1859 *m*/*z* (M); observed 255.10 (M−H)+*m*/*z*.

*4.2.6. (Z)-6-(2-(Trimethylsilyl)ethyl)octa-5,7-dien-1-ol (**17**).* To a −78 °C solution of vinyltrimethylsilane (0.431 mL, 2.94 mmol, 1 equiv) in 29 mL of diethyl ether (0.1 M) was added 2.94 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 2.94 mmol, 1 equiv) and 2.93 mL of

c-C_5H_9MgCl (2.01 M in ether, 5.88 mmol, 3 equiv) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **16** (0.256 g, 1 mmol, 0.34 equiv) in 2 mL THF (0.5 M) was added 0.465 mL of *n*-BuLi (2.54 M in hexanes, 1.18 mmol, 0.4 equiv) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. After concentration, the crude material was subjected to TBAF (1 mmol) in 10 mL THF. After stirred for 2 h, 10 mL of H_2O was added, and the product was extracted with 50 mL of EtOAc, dried over Na_2SO_4, and concentrated. *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (15% ethyl acetate: hexanes) to yield diene **17** as a clear oil (114.8 mg, 51%, *Z*:*E* 3:1). The stereochemistry of the major isomer was determined by NOE analysis. The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **17**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, *J*=11.2, 17.6 Hz, 1H), 5.41 (t, *J*=7.6 Hz, 1H), 5.22 (d, *J*=3.0 Hz, 1H), 5.08 (d, *J*=11.0 Hz, 1H), 3.65 (t, *J*=5.6 Hz, 2H), 2.20–2.15 (m, 2H+2H), 1.59–1.57 (m, 2H), 1.47–1.46 (m, 2H), 1.26 (br s, 1H), 0.70–0.65 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 132.8, 129.0, 113.2, 63.1, 32.5, 27.4, 27.2, 26.2, 16.1, −1.6; IR (thin film, NaCl) 3334, 3088, 2952, 1639, 1455, 1248, 1059, 990, 862, 837, 758, 690 cm^{-1}; HRMS (EI, Na) calcd for $C_{13}H_{26}OSi$, 226.1753 *m*/*z* (M); observed 226.1752 (M) *m*/*z*.

*4.2.7. (Z)-3-Trimethylsilylethyl-4-isopropyl-1,3-butadiene (**19**).* To a −78 °C solution of vinyltrimethylsilane (0.161 mL, 1.1 mmol) in 11 mL of diethyl ether (0.1 M) was added 1.1 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 1.1 mmol) and 1.1 mL of *c*-C_5H_9MgCl (2.06 M in ether, 2.2 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **18** (0.134 mL, 1.0 mmol) in 2 mL THF was added 0.440 mL of *n*-BuLi (2.50 M in hexanes, 1.1 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (hexanes) to yield diene **19** as a clear oil (96.2 mg, 50%, 20:1 *Z*:*E*). *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The stereochemistry of the major product was assigned by analogy to previous examples. The major alkene isomer was separated by HPLC [hexanes: 100% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **19**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, *J*=10.8, 17.3 Hz, 1H), 5.23–5.16 (m, 1H+1H), 5.06 (dd, *J*=1.6, 3.2 Hz, 1H), 2.75 (septet, *J*=6.6, 9.4, 13.3 Hz, 1H), 2.18–2.13 (m, 2H), 0.97 (d, *J*=8.0 Hz, 6H), 0.70–0.65 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.7, 133.2, 112.9, 27.3, 26.5, 23.4, 15.9, −1.6; IR (thin film, NaCl) 3444, 2956, 1731, 1248, 1177, 837, 758, 692, 468 cm^{-1}; HRMS (EI, M^+) calcd for $C_{12}H_{24}Si$, 196.1647 *m*/*z* (M); observed 197.1726 $(M+H)^+$ *m*/*z*.

*4.2.8. (Z)-1-Trimethylsilyl-3(cyclohexymethylene)pent-4-ene (**21**).* To a −78 °C solution of vinyltrimethylsilane (0.161 mL, 1.1 mmol) in 11 mL of diethyl ether (0.1 M) was added 1.1 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 1.1 mmol) and 1.1 mL of *c*-C_5H_9MgCl (2.00 M in ether, 2.2 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **20** (0.155 mL, 1 mmol) in 2 mL THF was added 0.440 mL of *n*-BuLi (2.50 M in hexanes, 1.1 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (hexanes) to yield diene **21** as a clear oil (125.7 mg, 53%, 20:1 *Z*:*E*). The stereochemistry of the major product was assigned by analogy to previous examples. The major alkene isomer was separated by HPLC [hexanes: 100% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **21**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, *J*=11.6, 17.2 Hz, 1H), 5.25–5.16 (m, 1H+1H), 5.06 (d, *J*=14.8 Hz, 1H), 2.44–2.36 (m, 1H), 2.18–2.14 (m, 2H), 1.69–1.54 (m, 2H+2H), 1.31–1.27 (m, 4H), 1.08–0.90 (m, 2H), 0.70–0.65 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.7, 133.3, 112.8, 36.4, 33.6, 33.0, 27.3, 26.1, 16.0, −1.5; IR (thin film, NaCl) 3417, 2854, 1714, 1450, 1248, 860, 758, 692 cm^{-1}; HRMS (EI, M^+) calcd for $C_{15}H_{28}Si$, 236.1960 *m*/*z* (M); observed 237.2042 (M+H) *m*/*z*.

4.3. Cross-coupling reactions of allenyl alcohols with styrene and chlorodimethyvinylsilane

*4.3.1. (Z)-6-(2-Phenylethyl)octa-5,7-dien-1-ol (**23**).* To a −78 °C solution of alkene **22** (0.182 mL, 1.92 mmol, 1 equiv) in 19.1 mL of diethyl ether (0.1 M) was added 1.92 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 1.92 mmol, 1 equiv) and 1.91 mL of *c*-C_5H_9MgCl (2.01 M in ether, 3.84 mmol, 3 equiv) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **16** (0.168 g, 0.65 mmol, 0.34 equiv) in 2 mL THF (0.5 M) was added 0.306 mL of *n*-BuLi (2.54 M in hexanes, 0.77 mmol, 1.1 equiv) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. After concentration, the crude material was subjected to TBAF (0.65 mmol) in 6.5 mL THF. After stirred for 2 h, 10 mL of H_2O was added, and the product was extracted with 50 mL of EtOAc, dried over Na_2SO_4, and concentrated. *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (15% ethyl acetate: hexanes) to yield diene **23** as a clear oil (120.4 mg, 52%, *Z*:*E* 2:1). The stereochemistry of the major isomer was determined by NOE analysis. The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **23**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 5H), 6.69 (dd, *J*=8.0, 17.6 Hz, 1H), 5.33–5.28 (m, 1H+1H), 5.14 (d, *J*=12.8 Hz, 1H), 3.62 (m, 2H), 2.78–2.74 (m, 2H), 2.51–2.47 (m, 2H), 2.21–2.15 (m, 2H), 1.55–1.51 (m, 2H), 1.42–1.40 (m, 2H), 1.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 136.1, 132.7, 131.1, 128.6, 128.4, 125.9, 113.4, 63.0, 35.5, 35.4, 32.4, 27.1, 26.0; IR (thin film, NaCl) 3351, 2932, 2860, 1635, 1603, 1495, 1454, 1059, 899, 747,

698 cm^{-1}; HRMS (EI, Na) calcd for $C_{16}H_{22}O$, 231.1671 *m*/*z* (M+H); observed 231.1755 $(M+H)^+$ *m*/*z*.

*4.3.2. 5-Methyl-3-methylenehex-4-en-1-ol (**25**).* To a −78 °C solution of alkene **24** (0.870 mL, 6 mmol) in 60 mL of diethyl ether (0.1 M) was added 6 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 6 mmol) and 6 mL of *c*-C_5H_9MgCl (2.01 M in ether, 12 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **10** (0.238 mL, 2 mmol) in 2 mL THF was added 0.880 mL of *n*-BuLi (2.54 M in hexanes, 2.2 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. After concentrated in vacuo, the crude material was purified by column chromatography on silica gel (hexanes) to yield diene as an impure, clear oil. This impure product was carried on to the subsequent step without further purification. The impure diene was dissolved in 10 mL 1:1 MeOH/THF, and $KHCO_3$ (8 mmol) and KF (16 mmol) were added. The reaction mixture was stirred for five additional minutes, 30% H_2O_2 (10.0 mmol) was added, and the reaction mixture was stirred for 17 h at room temperature. To the reaction was added aqueous $Na_2S_2O_3$ dropwise, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (15% ethyl acetate/hexanes) to yield diene **25** as a clear oil (128.4 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (s, 1H), 5.06 (s, 1H), 4.91 (s, 1H), 3.67 (dt, *J*=6.0, 12.0, 18.0 Hz, 2H), 2.35 (t, *J*=6.2 Hz, 2H), 1.80 (s, 6H), 1.38 (t, O–H, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 136.3, 125.3, 115.4, 61.2, 41.1, 26.8, 19.7; IR (thin film, NaCl) 3417, 2924, 1257, 1042, 799 cm^{-1}; HRMS (EI, M^+) calcd for $C_8H_{14}O$, 126.1045 *m*/*z* (M); observed 127.1127 $(M+H)^+$ *m*/*z*.

*4.3.3. (Z)-3-(Cyclohexylmethylene)pent-4-en-1-ol (**26**).* To a −78 °C solution of alkene **24** (0.416 mL, 3 mmol) in 30 mL of diethyl ether (0.1 M) was added 3 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 3 mmol) and 3 mL of *c*-C_5H_9MgCl (2.00 M in ether, 6 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **20** (0.115 mL, 1 mmol) in 2 mL THF was added 0.440 mL of *n*-BuLi (2.50 M in hexanes, 1.1 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before running through a silica plug and washing with 100 mL EtOAc. After concentrated in vacuo, the crude material was purified by column chromatography on silica gel (hexanes) to yield diene as an impure, clear oil. This impure product was carried on to the subsequent step without further purification. The impure diene was dissolved in 10 mL 1:1 MeOH/THF, and $KHCO_3$ (4 mmol) and KF (8 mmol) were added. The reaction mixture was stirred for five additional minutes, 30% H_2O_2 (5 mmol) was added, and the reaction mixture was stirred for 17 h at room temperature. To the reaction was added aqueous $Na_2S_2O_3$ dropwise, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (15% ethyl acetate/hexanes) to yield diene **26** as a clear oil (100.3 mg, 55%, 20:1 *Z*:*E*). The stereochemistry of the major product was assigned by analogy to previous examples. The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield analytically pure **26**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J*=11.0, 17.5 Hz, 1H), 5.31 (d, *J*=9.4 Hz, 1H), 5.24 (d, *J*=16.0 Hz, 1H), 5.11 (d, *J*=11.0 Hz, 1H), 3.68 (t, *J*=6.1 Hz, 2H), 2.47–2.43 (dt+m, *J*=1.0, 6.0, 12.7 Hz, 2H+1H), 1.73–1.62 (m, 4H), 1.31–1.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 132.8, 130.7, 113.8, 61.5, 36.7, 36.6, 33.6, 26.1, 26.0; IR (thin film, NaCl) 3418, 2852, 1727, 1449, 1267, 1122, 1042, 891, 737 cm^{-1}; HRMS (EI, M^++H) calcd for $C_{12}H_{20}O$, 181.1514 *m*/*z* (M+H); observed 181.1590 $(M+H)^+$ *m*/*z*.

*4.3.4. (Z)-3-(Cyclopentylmethylene)pent-4-en-1-ol (**28**).* To a −78 °C solution of alkene **24** (0.208 mL, 1.5 mmol) in 15 mL of diethyl ether (0.1 M) was added 1.5 mL of $ClTi(Oi\text{-}Pr)_3$ (1.00 M in hexanes, 1.5 mmol) and 1.5 mL of *c*-C_5H_9MgCl (2.00 M in ether, 3 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **27** (0.069 g, 0.5 mmol) in 2 mL THF was added 0.220 mL of *n*-BuLi (2.54 M in hexanes, 0.55 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd aq NH_4Cl solution. The mixture was warmed to room temperature before running through a silica plug and washing with 100 mL EtOAc. After concentrated in vacuo, the crude material was purified by column chromatography on silica gel (hexanes) to yield diene as an impure, clear oil. This impure product was carried on to the subsequent step without further purification. The impure diene was dissolved in 10 mL 1:1 MeOH/THF, and $KHCO_3$ (2 mmol) and KF (4 mmol) were added. The reaction mixture was stirred for five additional minutes, 30% H_2O_2 (2.5 mmol) was added, and the reaction mixture was stirred for 17 h at room temperature. To the reaction was added aqueous $Na_2S_2O_3$ dropwise, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* Selectivity was determined by ^1H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (15% ethyl acetate: hexanes) to yield diene **28** as a clear oil (44.1 mg, 53%, 20:1 *Z*:*E*). The stereochemistry of the major product was assigned by analogy to previous examples. The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **28**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, *J*=11.0, 17.6 Hz, 1H), 5.41 (d, *J*=9.0 Hz, 1H), 5.24 (dd, *J*=3.0, 17.5 Hz, 1H), 5.11 (d, *J*=11.0 Hz, 1H), 3.69 (t, *J*=6.4 Hz, 2H), 2.91–2.85 (m, 1H), 2.49 (t, *J*=8.8 Hz, 2H), 1.83–1.70 (m, 2H), 1.60–1.58 (m, 2H), 1.58–1.57 (m, 2H), 1.27–1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.9, 131.3, 113.7, 61.5, 38.5, 36.7, 34.2, 25.5; IR (thin film, NaCl) 3417, 2869, 1727, 1451, 1258, 1043, 842, 798, 471 cm^{-1}; HRMS (EI, M^+) calcd for $C_{11}H_{18}O$, 167.1358 *m*/*z* (M+H); observed 167.1437 $(M)^+$ *m*/*z*.

4.4. Preparation of isomeric allenes

*4.4.1. Synthesis of allene **30**.* To a solution of carbonyl diimidazole (1 equiv) in benzene (0.1 M) in a flame-dried round bottom flask, diol **29** (1 equiv) was added and the solution was refluxed under Ar for 17 h. Subsequently, the solution was cooled to room temperature, and water (10 mL) was added. The resulting mixture was extracted with ether, dried over $MgSO_4$, filtered, and concentrated by vacuum. The crude material was purified by column chromatography on silica gel (25% ethyl acetate/hexanes) to yield carbonate as a clear oil (87% yield). To a −78 °C solution of CuBr–Me_2S (2.381 g, 11.58 mmol) in 50 mL of THF was added 6.08 mL of *i*-PrMgCl 2.00 M

(12.16 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution was stirred at −78 °C for 1 h, then the carbonate of **29** (5.79 mmol, 1.339 g) in 10 mL THF was added dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, at −78 °C, then 5 mL of satd aq NH_4Cl was added. The mixture was warmed to room temperature before aqueous workup and extraction with 3×30 mL EtOAc. The crude material was purified by column chromatography on silica gel (10–30% ethyl acetate/hexanes) to yield allene **30** as a clear oil. (0.966 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.35–5.31 (m, 1H), 5.28–5.24 (m, 1H), 4.58 (s, 2H), 4.36–4.35 (m, 1H), 3.56 (dd, *J*=3.6, 9.6 Hz, 1H), 3.45 (dd, *J*=7.6, 9.6 Hz, 1H), 2.36–2.29 (m, 1H+1H), 1.00 (d, *J*=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 138.1, 128.6, 128.4, 127.9, 101.6, 93.0, 74.5, 73.6, 69.1, 27.9, 22.5; IR (thin film, NaCl) 3422, 2925, 1962, 1454, 1363, 1105, 873, 737, 698, 610 cm^{-1}; HRMS (EI, M^+) calcd for $C_{15}H_{20}O_2$, 232.1463 *m*/*z* (M); observed 231.1393 (M−H)+*m*/*z*.

*4.4.2. Synthesis of allene **32**.* To a solution of carbonyl diimidazole (1 equiv) in benzene (0.1 M) in a flame-dried round bottom flask, diol **31** (1 equiv) was added and the solution was refluxed under Ar for 17 h. Subsequently, the solution was cooled to room temperature and water (10 mL) was added. The resulting mixture was extracted with ether, dried over $MgSO_4$, filtered, and concentrated by vacuum. The crude material was purified by column chromatography on silica gel (25% ethyl acetate/hexanes) to yield carbonate as a clear oil (84% yield). To a −78 °C solution of CuBr–Me_2S (1.99 g, 9.66 mmol) in 50 mL of THF was added 5.07 mL of *i*-PrMgCl 2.00 M (10.14 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution was stirred at −78 °C for 1 h, then the carbonate of **31** (4.83 mmol, 1.117 g) in 10 mL THF was added dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, at −78 °C, then 5 mL of satd aq NH_4Cl was added. The mixture was warmed to room temperature before aqueous workup and extraction with 3×30 mL EtOAc. The crude material was purified by column chromatography on silica gel (10–30% ethyl acetate/hexanes) to yield allene **32** as a clear oil. (0.698 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.35–5.33 (m, 1H), 5.28–5.26 (m, 1H), 4.56 (s, 2H), 4.36 (m, 1H), 3.56 (dd, *J*=3.6 Hz, 9.6 Hz, 1H), 3.50 (dd, *J*=7.6, 9.6 Hz, 1H), 2.33–2.32 (m, 1H+1H), 1.01 (d, *J*=4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 138.1, 128.6, 128.0, 127.9, 101.9, 93.2, 74.4, 73.5, 68.8, 27.9, 22.6; IR (thin film, NaCl) 3392, 2960, 1962, 1725, 1454, 1364, 1076, 875, 743, 698 cm^{-1}; HRMS (EI, M^+) calcd for $C_{15}H_{20}O_2$, 232.1463 *m*/*z* (M); observed 231.1755 (M−H)+*m*/*z*.

4.5. Stereoselective access to (*Z*,*E*)- and (*Z*,*Z*)-1,3-dienes

*4.5.1. (2E,4Z)-1-Benzyloxy-4-hydroxyethyl-5-isopropyl-2,4-pentadiene (**33**).* To a −78 °C solution of alkene **24** (0.215 mL, 1.56 mmol) in 16 mL of diethyl ether (0.1 M) was added 1.56 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 1.56 mmol) and 1.56 mL of *c*-C_5H_9MgCl (2.01 M in ether, 3.12 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **30** (60.0 mg, 0.26 mmol) in 2 mL THF was added 0.112 mL of *n*-BuLi (2.54 M in hexanes, 0.286 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2 h, 5 mL of satd aq NH_4Cl solution was added. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (5% ethyl acetate/hexanes) to yield an impure diene as a clear oil. This impure sample was dissolved in 10 mL 1:1 MeOH/THF and $KHCO_3$ (1.04 mmol) and KF (2.08 mmol) were added. The reaction mixture was stirred for five additional minutes, 30% H_2O_2 (1.3 mmol) was added, and the resulting solution was stirred for 17 h at room temperature. To the reaction was added aqueous $Na_2S_2O_3$ dropwise, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* Selectivity was determined by ^{1}H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to yield diene **33** as a clear oil (38.8 mg, 52%, 5:1 *Z,E: Z,Z*). The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **33**. The stereochemistry of the major isomer was determined by NOE (see the analysis following the synthesis of **34**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 6.58 (d, *J*=15.9 Hz, 1H), 5.83 (dt, *J*=6.2, 12.3, 15.9 Hz, 1H), 5.29 (d, *J*=9.4 Hz, 1H), 4.54 (s, 2H), 4.11 (d, *J*=8.0 Hz, 2H), 3.68 (m, 2H), 2.81–2.75 (m, 1H), 2.45 (t, *J*=6.4 Hz, 2H), 1.29 (O–H, 1H), 0.99 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.4, 137.2, 129.5, 128.6, 128.0, 127.8, 126.0, 72.5, 71.3, 61.4, 37.4, 26.9, 23.4; IR (thin film, NaCl) 3391, 2958, 2866, 1454, 1360, 1043, 966, 736, 697, 470 cm^{-1}; HRMS (EI, Na) calcd for $C_{17}H_{24}O_2$, 261.1776 *m*/*z* (M+H); observed 261.1843 $(M+H)^+$ *m*/*z*.

*4.5.2. (2Z,4Z)-1-Benzyloxy-4-hydroxyethyl-5-isopropyl-2,4-pentadiene (**34**).* To a −78 °C solution of alkene **24** (0.142 mL, 1.03 mmol) in 11 mL of diethyl ether (0.1 M) was added 1.03 mL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.00 M in hexanes, 1.03 mmol) and 1.03 mL of *c*-C_5H_9MgCl (2.01 M in ether, 2.05 mmol) dropwise via gas-tight syringe. The resulting clear, yellow solution turned dark red-brown while warming to −50 °C over 1 h. The reaction mixture was stirred at −50 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **32** (79.5 mg, 0.34 mmol) in 2 mL THF was added 0.150 mL of *n*-BuLi (2.54 M in hexanes, 0.38 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the −78 °C solution of alkene dropwise via cannula. After warming slowly to 0 °C over 2.5 h, 5 mL of satd aq NH_4Cl solution was added. The mixture was warmed to room temperature before the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. The crude material was purified by column chromatography on silica gel (5% ethyl acetate/hexanes) to yield an impure diene as a clear oil. This impure sample was dissolved in 10 mL 1:1 MeOH/THF and $KHCO_3$ (1.37 mmol) and KF (2.73 mmol) were added. The reaction mixture was stirred for five additional minutes, 30% H_2O_2 (1.71 mmol) was added, and the resulting solution was stirred for 17 h at room temperature. To the reaction was added aqueous $Na_2S_2O_3$ dropwise, and the resulting solution was filtered through a plug of silica, eluting with 100 mL EtOAc. *Z*:*E* Selectivity was determined by ^{1}H NMR of the crude mixture after work-up. *Z*:*E* Selectivity was determined by ^{1}H NMR of the crude mixture after work-up. The crude material was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to yield diene as a clear oil (44.8 mg, 53%, 3:1 *Z,Z*:*Z,E*). The major alkene isomer was separated by HPLC [EtOAc/hexanes: 15–30% (0–30 min, 20 mL/min), on a Microsorb (Si 80-120 C5 H410119) column] to yield pure **34**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 6.00 (d, *J*=11.7 Hz, 1H), 5.77 (dt, *J*=6.6, 11.7, 13.1 Hz, 1H), 5.18 (d, *J*=9.7 Hz, 1H), 4.51 (s, 2H), 4.01 (d, *J*=8.0 Hz, 2H), 3.61 (t, *J*=11.7 Hz, 2H), 2.40–2.36 (m, 1H), 2.27 (t, *J*=6.2 Hz, 2H), 1.62 (O–H, 1H), 0.90 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.2, 130.6, 130.0, 128.6, 128.4, 128.1, 127.9, 72.9, 67.2, 60.1, 41.1, 28.2, 22.9; IR (thin film, NaCl) 3401, 3030, 2900, 2867, 1454, 1360, 1094, 1071, 736, 697, 608 cm^{-1}; HRMS (EI, Na) calcd for $C_{17}H_{24}O_2$, 261.1776 *m*/*z* (M+H); observed 261.1858 $(M+H)^+$ *m*/*z*.

Acknowledgements

We gratefully acknowledge financial support of this work by the American Cancer Society (RSG-06-117-01), the Arnold and Mabel

Beckman Foundation, Boehringer Ingelheim, Eli Lilly & Co., and the National Institutes of Health (GM080266).

Supplementary data

Complete experimental details for preparative procedures along with spectral data for all products are provided. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.02.062.

References and notes

1. For recent reviews, see: (a) Montgomery, J.; Sormunen, G. J. *Top. Curr. Chem.* **2007**, *279*, 1–23; (b) Ng, S.-S.; Ho, C.-Y.; Schleicher, K. D.; Jamison, T. F. *Pure Appl. Chem.* **2008**, 929–939; (c) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449; (d) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichemica Acta* **2008**, *41*, 95–104; (e) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394–1401; (f) Jeganmohan, M.; Chen, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876–10886; (g) Reichard, H. A.; McLaughlin, M.; Chen, M. Z.; Micalizio, G. C. *Eur. J. Org. Chem.* **2009**. doi:10.1002/ejoc.200901094
2. (a) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203–3206; (b) Gao, Y.; Harada, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5913–5916; (c) Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310–9313; (d) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699; (e) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441–4443; (f) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, F. *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569; (g) Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662–9663; (h) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221–4223; (i) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156–166; (j) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364–1367; (k) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443; (l) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342–15343; (m) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937–2940; (n) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077–3080; (o) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598–7610; (p) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664–4668; (q) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276; (r) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449; (s) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873–3876; (t) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432–8433; (u) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280–281; (v) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645; (w) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242–7243; (x) Cho, C.-W.; Skucas, E.; Krische, M. J. *Organomet.* **2007**, *26*, 3860–3867; (y) Hong, Y.-T.; Cho, C.-W.; Skucas, E.; Krische, M. J. *Org. Lett.* **2007**, *9*, 3745–3748; (z) Han, S. B.; Kong, J. R.; Krische, M. J. *Org. Lett.* **2008**, *10*, 4133–4135; (aa) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066–2067; (ab) Nevárez, Z.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 3773–3776; (ac) Bourque, L. E.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 5257–5260; (ad) Anderson, L. L.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 425–428; (ae) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694–3695; (af) Bahadoor, A. B.; Micalizio, G. C. *Org. Lett.* **2006**, *8*, 1181–1184.
3. For the coupling of two alkynes and an enone for the formation of a substituted cyclohexene, see: (a) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106–2107; For the coupling of cyclopropyl ketones to enones, see: (b) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348–5349; For the coupling of an imine with an enone, see: (c) Liu, L.; Montgomery, J. *Org. Lett.* **2007**, *9*, 3885–3887; For the coupling of an alkyne with an enone, see: (d) Herath, A.; Thompson, B. B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712–8713; For aldehyde–epoxide coupling, see: (e) Molinaro, C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 129–132; For enyne–epoxide coupling, see: (f) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130–4131; For the coupling of terminal alkenes to enones, see: (g) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893–1895; For the coupling of allenes with aldehydes, see: (h) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320–7321; (i) Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 11350–11359; For the coupling of aldehydes to terminal alkenes, see: (j) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 14194–14195; (k) Ng, S.-S.; Ho, C.-Y.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513–11528; (l) Ho, C.-Y.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 5362–5363; (m) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782–785; For coupling of a terminal alkene with an isocyanate, see: (o) Schleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, *9*, 875–878; For the coupling of *N*-sulfonyl imines with 2-vinylpyridines, see: (p) Komanduri, V.; Grant, C. D.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 12592–12593; For alkene–alkyne coupling, see: (q) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705 (and references cited therein); (r) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696–9697; (s) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032–12041; For the coupling of alkynes with enols, see: (t) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368–11369; For the coupling of allenes with enones, see: (u) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166–4167; (v) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466–12476; (w) Trost, B. M.; McClory, A. *Org. Lett.* **2006**, *8*, 3627–3629; For the coupling of 1,3-dienes to aldehydes or imines, see: (x) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033–4034; (y) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361; (z) Kojima, K.; Kimura, M.; Ueda, S.; Tamaru, Y. *Tetrahedron* **2006**, *62*, 7512–7520; For the coupling of homoallylic alcohols to acylpyrroles, see: (aa) Epstein, O. L.; Seo, J. M.; Masalov, N.; Cha, J. K. *Org. Lett.* **2005**, *7*, 2105–2108; For coupling of internal alkynes with allylic halides or allylic alcohols, see: (ab) Suzuki, N.; Kondakov, D. Y.; Kageyama, M.; Kotora, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519–4540; (ac) Takai, K.; Yamada, M.; Odaka, G.; Utimoto, K.; Fujii, T.; Furukawa, I. *Chem. Lett.* **1995**, 315–316.
4. For a discussion of the general design strategy, see Ref. 1g. For the coupling of an internal alkyne with a terminal alkyne, see: (a) Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005**, *7*, 5111–5114; (b) Perez, L. J.; Shimp, H. L.; Micalizio, G. C. *J. Org. Chem.* **2009**, *74*, 7211–7219; For the cross-coupling of two different internal alkynes, see: (c) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764–2765; For the coupling of internal alkynes with alkenes, see: (d) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440–1443; For the coupling of internal alkynes with imines, see: (e) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912–3914; (f) Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4982–4985; For the coupling of alkenes with imines, see: (g) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514–7516; For the coupling of allenes with alkynes, see: (h) Shimp, H. L.; Micalizio, G. C. *Chem. Commun.* **2007**, 4531–4533; (i) Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 6831–6837; For allylic alcohol–alkyne coupling, see: (j) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112–15113; For allene–imine coupling, see: (k) McLaughlin, M.; Shimp, H. L.; Navarro, R.; Micalizio, G. C. *Synlett* **2008**, 735–738; For allylic alcohol–vinylsilane coupling, see: (l) Belardi, J. K.; Micalizio, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 16870–16872; For allylic alcohol–imine coupling, see: (m) Takashi, M.; McLaughlin, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3648–3652; (n) Tarselli, M. A.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4596–4599; (o) Umemura, S.; McLaughlin, M.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 5402–5405; (p) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 17548–17549.
5. Internal alkynes and substituted alkenes are notoriously unreactive substrates in a variety of bimolecular metal-centered [2+2+1] chemistry. Examples that highlight the ability to overcome this characteristic include Refs. 4c,d,g,j,l,m–p.
6. Reichard, H. A.; Rieger, J. C.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 7837–7840.
7. Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340–348.
8. Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203–3206.
9. For study and application of related ylids, see the following selected references: (a) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827–2828; (b) Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B., III. *Synlett* **1998**, 765–767; (c) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961.
10. For examples of reductive cross-coupling chemistry with vinylsilanes, see: (a) Mizojiri, R.; Urabe, H.; Sato, F. *J. Org. Chem.* **2000**, *65*, 6217–6222; (b) Ref. 4l.
11. For the use of styrene in related Ti-mediated coupling reactions, see: (a) Lysenko, I. L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997–16002; For an early example of olefin exchange in the context of the Kulinkovich reaction, see: (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199.
12. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevsky, D. A.; Prityckaja, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244; (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.
13. Reductive ethylation processes have been reported in Ti-mediated reactions of EtMgBr with allylic ethers and allylic alcohols, see: (a) Kulinkovich, O. G.; Epstein, O. L.; Isakov, V. E.; Khmel'nitskaya, E. A. *Synlett* **2001**, 49–52; (b) Matyushenkov, E. A.; Churikov, D. G.; Sokolov, N. A.; Kulinkovich, O. G. *Russ. J. Org. Chem.* **2003**, *39*, 478–485 Also, the reductive ethylation of homoallylic alcohols has been reported; (c) Kulinkovich, O. G.; Shevchuk, T. A.; Isakov, V. E.; Prokhorevich, K. N. *Russ. J. Org. Chem.* **2006**, *42*, 659–664 See also, Ref. 11a..
14. In no case could a clean sample of (*Z*)-diene be obtained in any of attempted ethylation of an allenyl alcohol with EtMgBr.
15. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
16. Kang, S.-K.; Kim, S.-G.; Cho, D.-G. *Tetrahedron: Asymmetry* **1992**, *3*, 1509–1510.
17. This mechanistic proposal is consistent with the high levels of selectivity observed in related reductive cross-coupling reactions of allylic alkoxides with alkynes, vinylsilanes and imines (see Refs. 4j,4l,4m–o).
18. In comparison to the poor levels of reactivity associated with substituted alkenes in bimolecular metal-centered [2+2+1], Ti-mediated reactions of allenes are known: Hideura, D.; Urabe, H.; Sato, F. *Chem. Commun.* **1998**, 271–272.