Diastereoselective Carbometalation of Vinylmetals

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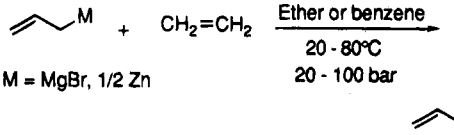
The allylzincation of vinylmetals is a very general reaction; whatever the nature of the vinyl organometallics, the reaction occurs with 1 equiv of substituted allylmagnesium bromide, if 1 equiv of zinc salt is present. This new synthetic approach leads to the creation of stereogenic secondary carbon centers with an excellent level of stereocontrol.

Reactions which result in the addition of the carbon–metal bond of an organometallic reagent across a carbon–carbon multiple bond leading to a new organometallic are called carbometalation reactions.[1] Although various carbometalation reactions of alkynes are known, the carbocupration has probably the largest synthetic possibilities,[2] conjointly with the zirconium-catalyzed carboalumination which allows the performance of methylaluminations.[3] Both alkenyl organometallics are able to form new carbon–carbon bonds with a variety of electrophiles and thus represent a new access to stereodefined C=C double bonds.[4] More severe reaction conditions are required for the carbometalation of alkenes. Most carbometalations of alkenes depend on the structure of the organic substrate,[1,5] and no general reaction for the intermolecular[6] carbometalation of alkenes is known. One particular example of carbometalation of alkenes is the addition of 2-alkenylmagnesium halides and bis(2-alkenyl)zinc to ethylene under pressure (20–100 bar) to give the corresponding 4-alkenylmetal compounds[7] (eq 1).



eq.1

In these allylmetalations of olefins, the authors have shown that the more substituted the olefin, the lower the reactivity.[8] One elegant solution to this problem has been found by Gaudemar[9] who reported that the addition of allylzinc bromide on substituted vinyl Grignard reagents leads to the organo-*gem*-bismetallic species. Although these organometallic compounds were obtained in moderate chemical yields, this reaction allows for the first time a very interesting approach to the synthesis of *gem*-bismetallic reagents[10] (eq 2). Some years later, it was found that a wide range of 1,1-bimetallic compounds[11] were available in high yields by carbometalation of alkenyl organometallics (magnesium or lithium) by allylic zinc bromide using reaction conditions similar to those described by Gaudemar. The different reactivity of the two metals present in compound **1** can be used to form

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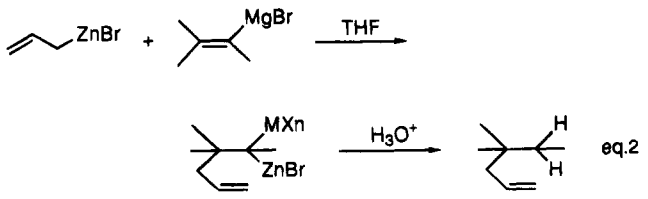
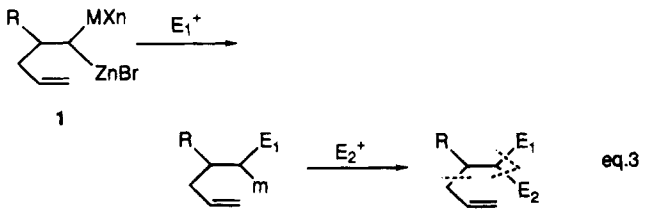


eq.2

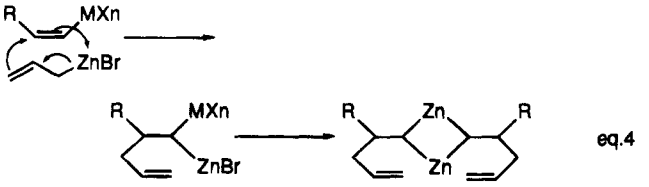
two new bonds with two appropriate electrophiles on the same carbon atom. The convergent aspect of this strategy (considered as a $a^2/d^1/d^1$ multicoupling reagent,[12] which is able to form successively three new bonds) represents a promising methodology in organic synthesis (eq 3). Although the exact mechanism of this reaction is



eq.3

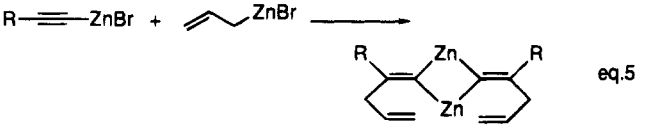
still under study, two hypotheses are taken into consideration.

Hypothesis 1. The addition of an allylic zinc bromide (or an allylic Grignard reagent instead of the zinc derivative, provided one zinc salt equivalent is present in the reaction mixture) to a vinyllithium or magnesium reagent leads to the *gem*-bismetallic by a carbometalation process via a transition state corresponding to a zinca ene reaction[13] (eq 4). It seems plausible that, especially



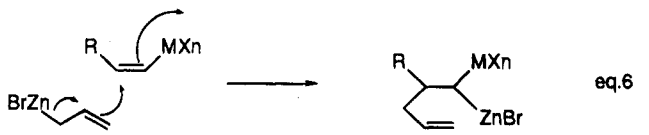
eq.4

in the case of MX_n = Li, the coexistence of an organolithium with an organozinc bromide on the same carbon atom should lead to a dizincacyclobutane by a dimerization process. The bismetalla four-membered ring is common, for example, in the alkoxide structures.[14] Moreover, a similar dimeric compound was postulated by reaction of an alkynyl zinc bromide reagent with an allylzinc bromide[15] (eq 5). Instead of this suprafacial



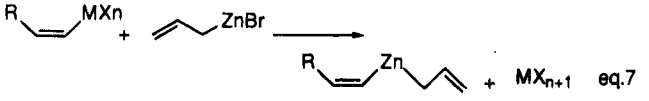
eq.5

addition (eq 4), one should also consider a possible anti addition analogous to the Felkin[5k,l] reaction, in the case of the addition of allylmagnesium bromide on the C=C double bond of allyl alcohols (eq 6).



eq.6

Hypothesis 2. The first step of this reaction is the formation of a mixed zinc species with a salt displacement. It is known to be fast for MX_n = Li but slower with MX_n = MgX (eq 7). This allylvinylzinc leads to a



eq.7

gem-bismetallic species if 2 mol are implied in a bishomomolecular process. This latter process can occur either via a linear mixed zinc species (path a) or via a bishomomolecular process involving an internal rearrangement akin to the Claisen rearrangement where zinc plays the role of oxygen (path b). Path a corresponds to a *syn* addition to the C=C double bond whereas path b represents an *anti* addition (eq 8).

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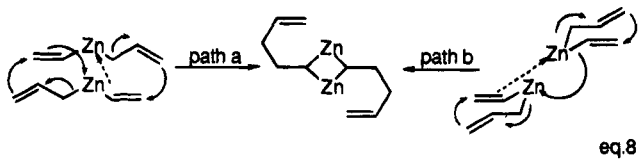
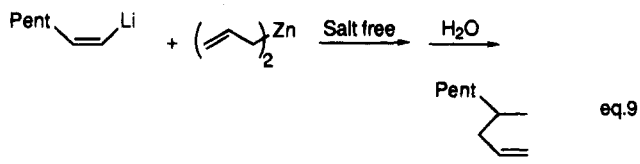


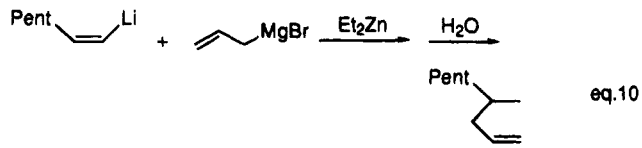
eq.8

The scope of this reaction is quite broad: (1) Whatever the nature of the vinyl organometallics, -organolithium, -magnesium, -aluminum, -boron, or -copper reagent, the reaction occurs with 1 equiv of allylmagnesium bromide, if 1 equiv of zinc salt (or cadmium salt) is present, and is not catalytic with Zn^{II}. (2) Pure bisallylzinc,[16] in the presence of a salt-free vinyllithium, also gives the reaction, probably via a zincate complex: thus, the presence of lithium or magnesium halides is not a requirement for the reaction to proceed, and activation of the C=C bond by a Lewis acid is ruled out (eq 9). (3) In a similar



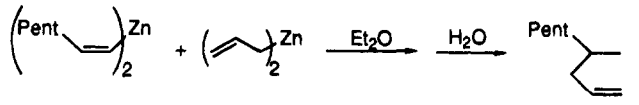
eq.9

way, a vinyllithium in the presence of allylmagnesium bromide and Et_2Zn (instead of zinc salt) leads also to the bismetallic species (eq 10). (4) Pure bisallylzinc[16] and bis-



eq.10

(vinyl)zinc also give the reaction (eq 11).



eq.11

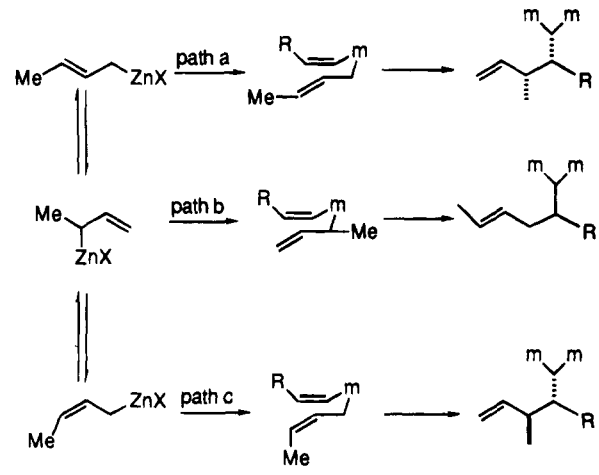
Thus, whatever the initial zincated species are, redistribution equilibria occur probably very fast to form the reactive species which then undergoes the addition leading to the organobismetallic species. This points to a possible formation of a zincate of zinc[17] even if it cannot be detected by NMR measurements.

In the absence of more physical data, we shall consider, in the following, that the more plausible working hypothesis is represented by eq 8, path b. For the sake of simplicity we shall represent the bismetallic species thus formed as a monomer (eq 12).

eq. 12

Diastereoselection. The Claisen or Ireland–Claisen rearrangement is a highly useful transformation in acyclic diastereoselection.[18] The stereochemical outcome of the rearrangement is controlled by the geometry of the remote olefin and of the enolate.[19] If we consider the carbometalation transition state, the addition of substituted allylic systems with a stereochemically pure alkenylmetal can generate (eq 12), at least, three products according to the metallotropic rearrangements of the substituted allylic system (Scheme 1).

Scheme 1



Indeed, if the crotylzinc bromide, the simple substituted allylic system, reacts under its *E* configuration (path a, Scheme 1), we obtain a vinylcrotylzinc where the crotyl moiety displays a pseudoequatorial methyl group in a chairlike transition state to afford a *gem*-bismetallic compound where the two substituents are in a *syn* relationship.

On the other hand, if the crotylzinc bromide reacts with the same vinylmetal under its secondary position (path b, Scheme 1), we obtain also a vinylcrotylzinc intermediate, but in this case, the methyl group will end up in a vinylic position.

Finally, if the crotylzinc reacts under its *Z* configuration (path c, Scheme 1) the crotyl moiety displays a pseudoaxial methyl group in a chairlike transition state to afford, after the [3,3] sigmatropic rearrangement, an organogembismetallic reagent where the two substituents are in an *anti* relationship to each other.

Thus, for a vinyl metal of determined stereochemistry, the diastereoselectivity resulting from the carbometalation process will be only dependent of the metallotropic equilibrium of the substituted allylic system (path a versus b versus c, Scheme 1).

Preliminary experiments from these laboratories were carried out by addition of the 2-butenylzinc bromide to the pure (*Z*)-heptenyllithium in THF[11b] leading after hydrolysis to the alkene **5** as a mixture of two diastereoisomers in a 1:1 ratio. This diastereoselection was improved by replacement of the 2-butenylzinc bromide by the 2-octenylzinc bromide.[11b]

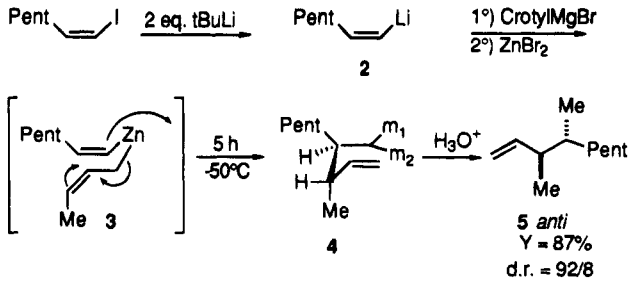
(16) (a) Zakharkin, L. I.; Yu Okhlobystin, O. *Zh. Obshch. Khim.* **1960**, *30*, 2134. (b) Thiele, K. H.; Zdunneck, P. *J. Organomet. Chem.* **1965**, *4*, 10.

(17) (a) Fabicon, R. M.; Pajerski, A. D.; Richey, Jr. H. G. *J. Am. Chem. Soc.* **1991**, *113*, 6680–6681. (b) Nimler, J. W.; Cook, T. H. *J. Chem. Phys.* **1973**, *58*, 1596.

(18) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, 1. (b) Kahns, D.; Hehre, W. J. *J. Org. Chem.* **1988**, *53*, 301–305. (c) Cha, J. K; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263–5266. (d) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (e) Sparks, M. A.; Panek. J. S. *J. Org. Chem.* **1991**, *56*, 3431–3438. (f) Denmark, S. E.; Stadler, H.; Dorow, R. L.; Kim, J. H. *J. Org. Chem.* **1991**, *56*, 5063–5079.

(19) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975–3978. (c) Tadano, K. I.; Minami, M.; Ogawa, S. *J. Org. Chem.* **1990**, *55*, 2108–2113. (d) Kurth, M. J.; Beard, R. L. *J. Org. Chem.* **1988**, *53*, 4085–4088.

Scheme 2



Since then, we have observed that the diastereoselection is highly dependent on the temperature and the nature of the solvent. Thus, decreasing the Lewis basicity of the solvent, by switching from THF to ether, considerably speeds up the reaction and allows the addition to be carried out at much lower temperatures. Under these conditions, crotylzinc bromide leads to very high diastereoselections at −50 °C within 5 h.

Starting from a pure 1(*Z*)-iodo-1-heptene,[2a,20] metal−halogen exchange[21] affords an alkenyllithium reagent **2**, which reacts with crotylmagnesium bromide and zinc dibromide in ether to give the postulated crotylvinylzinc compound **3** which then undergoes, at −50 °C, the addition, leading to the stable 1,1-dimetallic species **4** and, after acidic hydrolysis, to the 3(*S**),4(*R**)-dimethyl non-1-ene **5** *anti* in 87% yield with a diastereoselection of 92/8[22] (Scheme 2).

The high diastereoselectivity observed in the rearrangement of **3** may be accounted for by a preferential[23] or kinetically favored *Z* configuration of the crotylmetal species, if we consider a chairlike transition state. If we compare this reaction with the allyl zincation of 1-octene, as described by Lehmkuhl et al.[8] where octene is the solvent (eq 13), the latter requires 66−96 h at 50 °C.

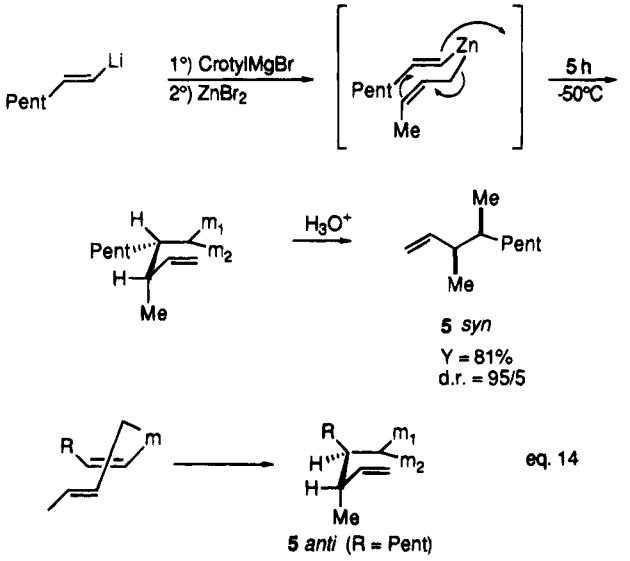
eq. 13

Thus, metalation of the olefin has a tremendous effect, which may be interpreted in terms of a good ability for zinc to bridge carbon atoms.

The other diastereoisomer 3(*S**),4(*S**)-dimethylnon-1-ene **5** *syn* is very easily obtained, with a very high diastereomeric purity, only by changing the stereochemistry of the vinyllithium[24] (Scheme 3).

In the two preceding examples, the stereochemical outcome is explained by the *Z* configuration of the crotylmetal species in the chairlike transition state. However, this result can be also explained by the *E* configuration of the crotylmetal species in a boat like transition state (eq 14).

Scheme 3



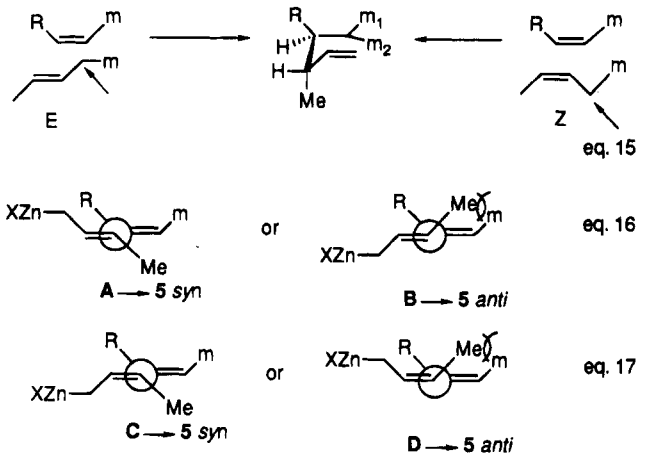
eq. 14

In acyclic systems, the Claisen rearrangements show a well-established preference for chairlike transition states.[18a,19] This preference is even more pronounced in the Cope rearrangement.[25] Thus, by analogy with the litterature data, the transition state of this carbometalation reaction will be considered as a chairlike transition state. The preferred *Z* configuration of substituted allylic cations derived from Cs or K is well described in the literature,[23c,26] and it is generally accepted that the more covalent the carbon−metal bond, the more the *E* configuration prevails. However, contradictory results have been disclosed concerning the NMR study of crotylzinc species: Thiele et al.[27] showed that the reagent was purely σ bonded to zinc[28] with a cis structure (J_{H-H} = 12 Hz). However, Lemkuhl et al.[29] considered a rapid equilibrium where this *J* value was an average of the trans structure (J_{H-H} = 16 Hz) and the cis structure (J_{H-H} = 10 Hz) confirming the predominance of the latter.

Thus, the high ratio of **5** *anti* should be attributed to a kinetic preference of the *cis*- crotylzinc species in the transition state. Nevertheless, according to hypothesis 1 (eq 4), the formation of the organo-*gem*-bismetallic can also be rationalized by a simple allyl metalation, as a zinca ene reaction, of the vinylzinc reagent. In this case, the difference between the two following transition states (crotylmetal with *E* or *Z* configuration) is very slight (eq 15) and involves mostly the position of the metal-bearing CH_2 group.

At this point, one should consider another hypothesis where an "open transition state" could be invoked, with the E or Z crotyl reagent. The *E* reagent leads to transitions states **A** or **B** (eq 16), but the less hindered

(20) Alexakis, A.; Cahiez, G.; Normant, J.-F. *Org. Synth.* **1984**, *62*, 1−8.
(21) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1−46.
(22) Marek, I.; Lefrançois, J. M.; Normant, J. F. *Synlett* **1992**, 633−635.
(23) (a) Agami, C.; Andrac-Taussig, M.; Prevost, C. *Bull. Soc. Chim. Fr.* **1966**, 2596. (b) Oppolzer, W.; Pitteloud, R.; Strauss, H. F. *J. Am. Chem. Soc.* **1982**, *104*, 6476. (c) Schleyer, P. v. R.; Kaneti, J.; Wu, Y. D.; Chandrosekhar, J. *J. Organomet. Chem.* **1992**, *426*, 143 and references cited therein. (d) Hutchinson, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 7075−7082.
(24) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424.
(25) (a) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; 503. (b) Blechert, S. *Synthesis* **1989**, 71−82.
(26) (a) Schlosser, M. *Modern Synth. Meth.* Scheffold, R., Ed.; **1992**, 227−271. (b) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893−5895. (c) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Frazer, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426−1429.
(27) Thiele, K. H.; Engelhardt, G.; Koller, J.; Arnstedt, M. *J. Organomet. Chem.* **1967**, *9*, 385−393.
(28) Zinc compounds have a monohapto to organometallic σ-bond. (a) Hoffmann, E. G.; Nehl, A.; Lehmkuhl, H.; Seevojel, K.; Stempfle, W. *Chem. Ber.* **1984**, *117*, 1304. (b) Blom, R.; Haaland, A.; Weidlein, J. *J. Chem. Soc., Chem. Commun.* **1985**, 266−267.
(29) Benn, R.; Hoffmann, E. G.; Lehmkuhl, H.; Nehl, H. *J. Organomet. Chem.* **1978**, *146*, 103−112.



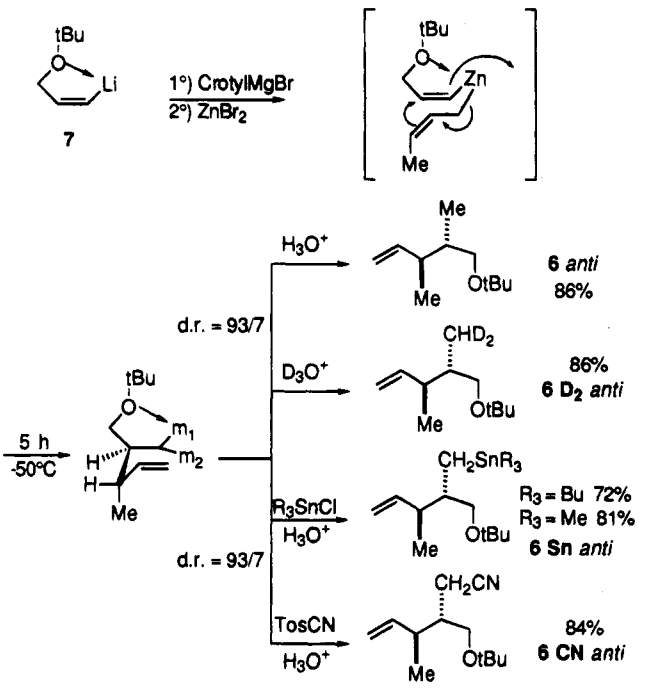
one **A** leads to the wrong isomer. The *Z* reagent leads to transition states **C** or **D** (eq 17), and the less hindered one also leads to the *syn* isomer of **5**.

Taking into consideration the very high diastereoselectivity observed here, we postulate that the more compact the transition state, the better the diastereoselection. Then, the cyclic transition state, with the *Z* configuration of the crotylmetal species, as described in the carbometalation reaction (path c, Scheme 1) will be preferred as to now to explain our results. In a second step, we studied the case[22] of functionalized vinyllithiums.[30] A stronger chelation of the zinc atom should not be favorable if we consider the detrimental effect of THF as compared to ether (Scheme 4).

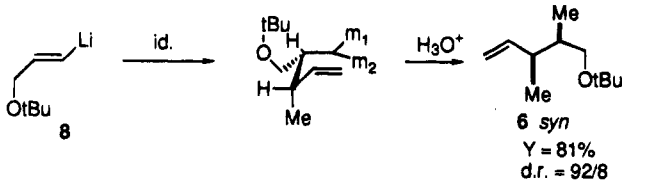
However, in spite of the chelation of the zinc atom by the *tert*-butoxy group, this substrate undergoes the [3,3] rearrangement at a very low temperature to give, after acidic hydrolysis, the (2*S**,3*S**)-dimethyl-1-*tert*-butoxy pent-4-ene **6** *anti* with a very high diastereoselectivity (93/7) and good chemical yield (yield = 86%). The formation of the *gem*-bismetallic species has been proved by quenching the intermediate with DCl to afford the *gem*-dideuterio **6 D_2** *anti* compound. In a similar fashion, subsequent treatment of the *gem*-bismetallic reagent with 1 equiv of trialkyltin chloride and hydrolysis gives the stannylated **6 Sn** *anti* with an excellent purity. Finally, the reaction of the bimetallic reagent with TosCN[31] produces selectively, after hydrolysis, the nitrile **6 CN** *anti* in 84% yield.

The easy preparation of the corresponding E vinyllithium[32] leads, according to the same procedure, to the *syn* diastereoisomer (Scheme 5). The configuration of **6** *anti* is established[33] by comparison with the analogous product derived from a known[34] Ireland–Claisen rearrangement and shows a slightly higher purity via our route (Scheme 6).

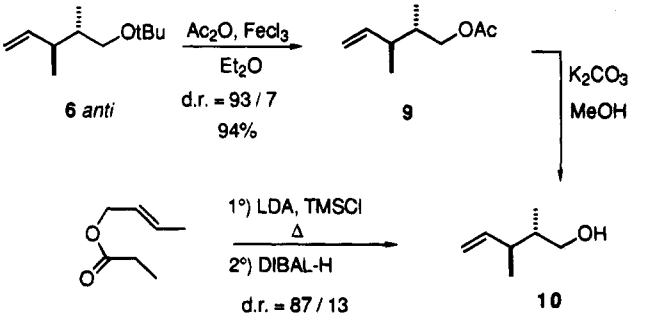
Scheme 4



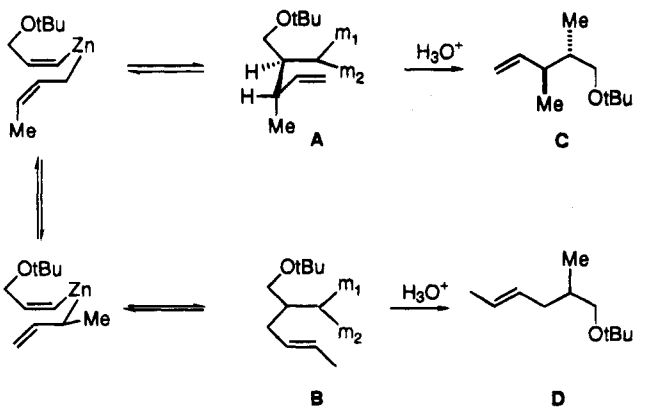
Scheme 5



Scheme 6



Scheme 7



During this study, we also observed that such addition is, in fact reversible (Scheme 7). If the mixture is left at room temperature overnight, or heated for a few hours,

(30) Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243–6246.

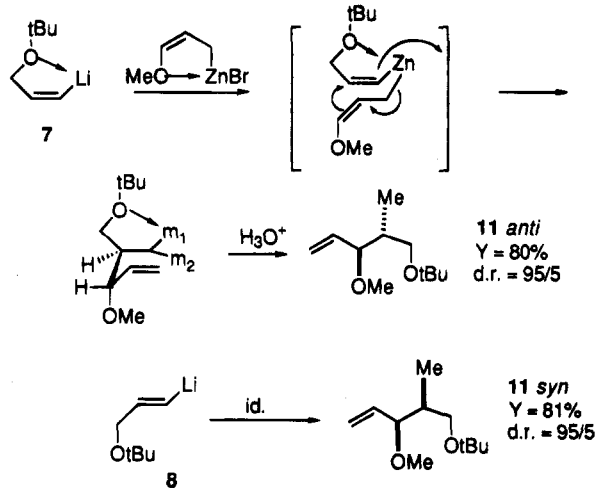
(31) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623–4626.

(32) Prepared by hydroalumination of 1-(trimethylsilyl)propargyl *tert*-butyl ether, in ether, in the presence of 1 equiv of Et_3N (to prevent the isomerization described by: Miller, J. A.; Negishi, E. I. *Isr. J. Chem.* **1984**, *24*, 76) followed by desilylation with MeONa/MeOH: On, H. P.; Lewis, W.; Zweifel, G. *Synthesis* **1981**, 999–1001.

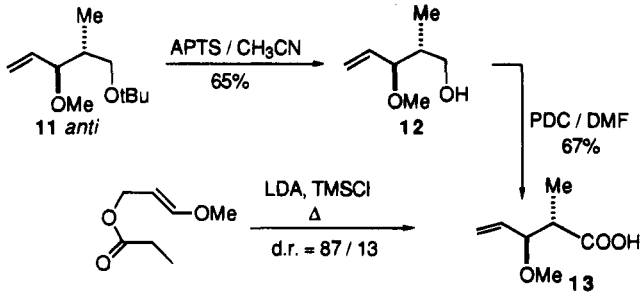
(33) Deprotection of the *tert*-butoxy group into the acetate: (a) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728. (b) Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951.

(34) (a) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572–3582. (b) Tsunoda, T.; Sasaki, O.; Ito, S. *Tetrahedron Lett.* **1990**, *31*, 727–730. (c) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sakao, Y.; Hondo,Y.; Ito, S. *Tetrahedron Lett.* **1992**, *33*, 1651–1654. (d) Oh, T.; Wrobel, Z.; Devine, P. N *Synlett* **1992**,81–83.

Scheme 8



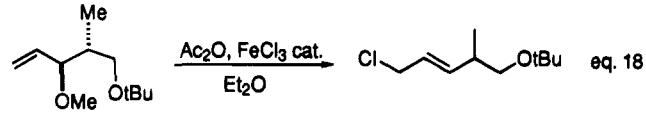
Scheme 9



A is converted to **B** and hydrolysis leads to a 1/1 mixture of **C** and **D**. This is of no concern for the reaction depicted in the Schemes 2–5, carried out at low temperature, but will be important for other substrates leading to sluggish reactions. This methodology can be tested on more functionalized molecules. Thus, introduction of an allylic methoxy group, instead of a methyl, is possible if one starts from the allyl methyl ether metalated according to Evans,[7d,35] and reacted with **7** or **8** (Scheme 8).

In our case, the metalation of the allyl methyl ether is carried out in ether with 1 equiv of TMEDA. The chelation of this diamine on the reactive species, hetero-substituted-allylvinylzinc, decreases considerably the kinetic of this reaction, and now the [3,3] sigmatropic rearrangement occurs at room temperature in 24 h. Nevertheless, in each case, the *syn* or *anti* 1,3-glycol diether is obtained diastereoselectively (Scheme 8). The relative stereochemistry of the substituents is determined by correlation with the product obtained by the Ireland–Claisen method.[34] Here again, this approach gives better diastereoselection than the latter one (yield = 61%; dr = 87/13, Scheme 9).

The same stereochemical outcome has been observed[36] when treating a THF solution of this heterosubstituted allylic zinc bromide and 1-octenylmagnesium bromide. During this determination of stereochemistry by correlation, we have observed that the deprotection of the *tert*-butoxy ether by the $FeCl_3$, Ac_2O method,[33] leads to a substitution of the allylic methoxy ether by a halogen without deprotection of the *tert*-butoxy ether (eq 18).



A similar result has been observed by Johnson[37] in the case of allylic *tert*-butoxy ethers. However, we have found that exposure of primary or secondary *tert*-butoxy ethers, in an allylic position or not, with 1 equiv of APTS in acetonitrile leads directly to the alcohol.[38] This represents a new and mild method for *tert*-butoxy ether deprotection. The metalated allyl methyl ether reacts also with the pure 1(*Z*)-lithio-1-heptene (**2**) to give the stable 1,1-dimetallic species in 24 h at room temperature, which can subsequently react with 1 equiv of tributyltin chloride, followed by an acidic hydrolysis to give **14** with 77% chemical yield and with a 95/5 diastereomeric ratio (Scheme 10).

The worst case is provided with metallated allyl sulfides. The cis lithiated allyl ether **7** undergoes the addition of the metalated allyl phenyl sulfide[39] to give a mixture of products (Scheme 11). Both regioisomers are formed at 10 °C, in a slow reaction (**15**: yield = 30%, dr = 50/50; **16**: yield = 50%, *E*/*Z* = 60/40) and at 25°C, for 24 h, the organogembismetallic precursor of **15** cyclizes to a cyclopropane[11b] **17** in 95% yield (dr = 70/30).[40] These different results are well explained by the reversibility of the carbometalation (see Scheme 7). The presence of **16**, observed for the first time in this reaction, is explained by the intermediate depicted in the general Scheme 1, according to path b (with PhS instead of Me).

Conclusion

The allylzincation of vinylmetals is a very general reaction, with regard to the nature of the vinylmetal and to the nature of the allylic metal, provided 1 equiv of zinc salt is present in the reaction mixture. This new methodology is amenable to proceed highly diastereoselectively from properly hetero-substituted partners, at low temperature and with good chemical yields. It represents a new synthetic approach to construct adjacent stereogenic centers, by the metallotropic equilibrium of the allylic substituted substrate—an issue rarely examined in the carbometalation of olefins.[5n] The *syn*/*anti* relationship can be simply modulated from the *E* or *Z* nature of the starting vinylmetal.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a JEOL 400 MHz or a Brucker AC 200 apparatus ($CDCl_3$; δ ppm from TMS). GLPC analyses were performed on a Carlo Erba chromatograph Model G1 and 2150 using a 25-m capillary glass column (OV 101). The gas chromatograph was coupled to an integrator Hitachi D 2000. Microanalyses were obtained from the University Pierre et Marie Curie laboratories.

3(*S),4(*R**)-Dimethylnon-1-ene (5 *anti*).** To a solution of 1(*Z*)-iodohept-1-ene[20] (500 mg, 2.2 mmol) in Et_2O (30 mL) was added at −78°C, 2 equiv of *tert*-BuLi (1.6 M solution in

(35) (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560–5561. (b) Still, W. C.; Mac Donald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561–5563. (c) Yamamoto, Y. *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon Press: New York, 1991, Vol. 2, p 55.

(36) Knochel, P.; Xia, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29*, 6697–6700.

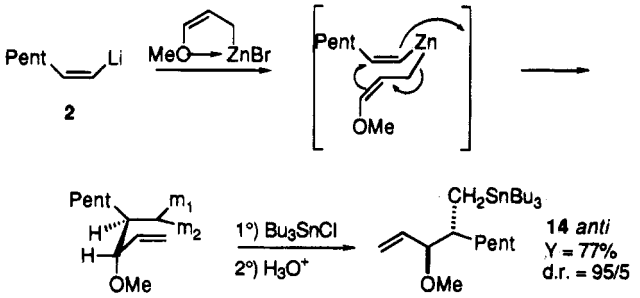
(37) Bartlett, W. R.; Johnson, W. S.; Plummer, M. S.; Small, V. R., Jr. *J. Org. Chem.* **1990**, *55*, 2215.

(38) Currently under study.

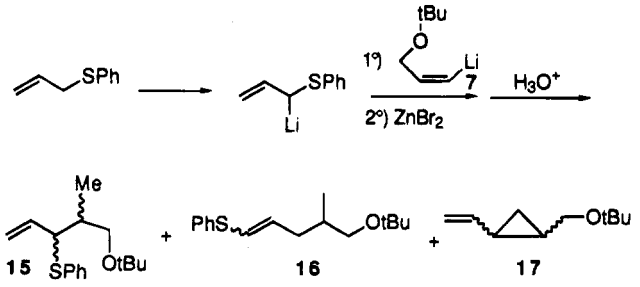
(39) (a) Brandsma, L. *Preparative Polar Organometallic Chemistry*, 2nd ed.; Springer-Verlag: New York, 1990, p 105. (b) Ikeda, Y.; Furuta, K.; Meguriya, N. Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *44*, 7663–7665. (c) Biellmann, J. F.; Ducep, J. B. *Tetrahedron Lett.* **1968**, 5629–5630. (d) Yamamoto, Y.; Yatagai, H.; Saito, Y.; Maruyama, K *J. Org. Chem.* **1984**, *49*, 1096–1104.

(40) The relative stereochemistry of the cyclopropane was not determined.

Scheme 10



Scheme 11



hexane, 2.8 mL, 4.4 mmol). This solution was warmed to −65 °C for 10 min to complete the lithium−iodine exchange, and then, at −65 °C, 1.5 equiv of crotylmagnesium bromide was added (1 M solution in Et_2O, 3.3 mL, 3.3 mmol) and 1.5 equiv of $ZnBr_2$ in Et_2O was slowly added at −60 °C (1 M solution in Et_2O, 3.3 mL, 3.3 mmol). The reaction mixture was stirred at −50 °C for 5 h, and the quantitative formation of the adduct **5** was checked by GC. The hydrolysis was done with an aqueous solution of hydrochloric acid (1 N solution, 20 mL). The aqueous phase was extracted twice with ether (2 × 20 mL), and the combinated organic phases were washed with HCl 1 N (2 × 20 mL). The organic layer was treated overnight with an aqueous solution of Na_2S and then washed with $NaHCO_3$ (2 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 (eluent: pentane only): yield of **5** 87% (295 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 4.96 (dd, 2H, J = 11.8, 4.95 Hz), 2.2 (m, 1H), 1.4 (m, 8H), 0.97 (d, 3H, J = 6.6 Hz), 0.89 (t, 3H, J = 6.6 Hz), 0.81 (d, 3H, J = 7.15 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 113.4, 42.2, 37.7, 34.0, 32.2, 27.0, 22.7, 17.3, 15.9, 14.1. Anal. Calcd for $C_{11}H_{22}$: C, 85.63; H, 14.37. Found: C, 84.82; H, 15.36.

3(S*),4(S*)-Dimethylnon-1-ene (5 *syn*). The same procedure as above was used, starting with 1(*E*)-iodohept-1-ene[24] (500 mg, 2.2 mmol); yield 275 mg (81%); ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, 1H, J = 9.35, 17.6, 7.14 Hz), 4.95 (d, 2H, J = 15.4 Hz),2.1 (m, 1H), 1.4 (m, 8H), 0.93 (d, 3H, J = 6.6 Hz), 0.89 (t, 3H, J = 6.6 Hz), 0.81 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 143.9, 112.8, 42.2, 37.5, 34, 32.1, 27.1, 22.7, 15.8, 15.3, 14.1.

2(S*),3(S*)-dimethyl-1-*tert*-butoxypent-4-ene (6 *anti*). The same procedure as above was used, starting with 1(*Z*)-iodo-3-*tert*-butoxyprop-1-ene[30] (500 mg, 2.1 mmol). The residue was chromatographed on SiO_2 (eluent: cyclohexane/ethyl acetate 98/2): yield 303 mg (86%); ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, 1H, J = 9.7, 17.3, 7.1 Hz), 5 (d, 2H, J = 11.4 Hz), 3.2 (dd, 1H, J = 6.6, 6.6 Hz), 3.10 (dd, 1H, J = 6.6, 6.6 Hz), 2.3 (m, 1H), 1.6 (m, 1H), 1.10 (s, 9H), 1 (d, 3H, J = 7.15 Hz), 0.83 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 113.9, 72.2, 65.0, 39.0, 38.5, 27.5, 17.8, 13.0. Anal. Calcd for $C_{11}H_{22}O$: C, 77.57; H, 13.02. Found: C, 77.98; H, 13.18.

2(S*)-Dideuteriomethyl-3(S*)-methyl-1-*tert*-butoxypent-4-ene (6 D_2 *anti*). The same procedure as above was used, but the hydrolysis was done with an excess of DCl; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, 1H, J = 9.7, 17.3, 7.1 Hz), 5 (d, 2H, J = 11.4 Hz), 3.2 (dd, 1H, J = 6.6, 6.6 Hz), 3.10 (dd, 1H, J = 6.6, 6.6 Hz), 2.3 (m, 1H), 1.6 (m, 1H), 1.10 (s, 9H), 1 (d, 1H, J = 7.15 Hz), 0.83 (d, 3H, J = 6.6 Hz).

2(S*)-[(Trimethylstannio)methyl]-3(S*)-methyl-1-*tert*-butoxypent-4-ene (6 Sn *anti*). The same procedure as **6** *anti* was used, but after quantitative formation of the bismetallic, 1 equiv of trimethyltin chloride was added at −30 °C (2.1 mmol, 415 mg). The reaction mixture was stirred 30 min at −30 °C and warmed to 0 °C in 2 h. The hydrolysis was done with an aqueous solution of HCl 1 N (20 mL), and after usual treatment, the residue was chromatographed on SiO_2 (cyclohexane/ethyl acetate 98/2): yield 81% (560mg); ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (m, 1H), 4.98 (dd, 2H, J = 11.8, 17 Hz), 3.1 (dd, 1H, J = 6.6, 6.6 Hz), 2.95 (dd, 1H, J = 6.6, 6.6 Hz), 2.3 (m, 1H), 1.6 (m, 1H), 0.95 (s, 9H), 0.85 (d, 3H, J = 7 Hz), 0.76 (dd, 1H, J = 4, 10.5 Hz), 0.62 (dd, 1H, J = 4, 10 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.1, 113.8, 72.3, 65.0, 42.1, 40.7, 27.5, 26.9, 17.1, 11.2, −8.8. Anal. Calcd for $C_{14}H_{30}OSn$: C, 50.48; H, 9.07. Found: C, 51.21; H, 8.93.

2(S*)-[(Tributylstannio)methyl]-3(S*)-methyl-1-*tert*-butoxypent-4-ene (6 Sn *anti*): yield 72% (672 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 4.96 (d, 2H, J = 11.4 Hz), 3.1 (dd, 1H, J = 6.6, 6.6 Hz), 2.4 (m, 1H), 1.7 (m, 1H), 1.5 (dt, 6H, J = 5.8, 9.54 Hz), 1.3 (q, 6H, J = 7.34 Hz), 1.18 (s, 3H), 0.9 (t, 9H, J = 7.34 Hz), 0.8 (dd, 6H, J = 10, 2.1 Hz), 0.58 (dd, 1H, J = 4, 10 Hz).

2(S*)-(Cyanomethyl)-3(S*)-methyl-1-*tert*-butoxypent-4-ene (6 CN *anti*). The same procedure as **6** *anti* was used, but after quantitative formation of the bismetallic, *p*-toluenesulfonyl cyanide (380 mg, 2.1 mmol) was added at −30 °C. After being warmed to 0 °C for 1 h, the reaction mixture was hydrolyzed as above. The residue was chromatographed on SiO_2 (cyclohexane/ethyl acetate 90/10): yield 84% (340 mg); ^1H NMR (200 MHz, $CDCl_3$) δ 5.65 (m, 1H), 5.1 (dd, 2H, J = 12, 16 Hz), 3.55 (dd, 1H, J = 11.8, 6 Hz), 3.4 (dd, 1H, J = 8.8, 11.8 Hz), 2.5 (dd, 2H, J = 16, 8.5 Hz), 2.3 (m, 1H), 1.7 (m, 1H), 1.2 (s, 9H), 1.05 (d, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.2, 119.0, 115.4, 72.7, 60.1, 40.7, 38.5, 27.3, 17.5. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.83. Found: C, 74.08; H, 11.42.

2(R*),3(S*)-Dimethyl-1-*tert*-butoxypent-4-ene (6 *syn*). The same procedure as above was used, starting with 1(*E*)-iodo-3-*tert*-butoxyprop-1-ene:[32] yield 287 mg (81%); ^1H NMR (200 MHz, $CDCl_3$) δ 5.7 (m, 1H), 4.97 (dd, 2H, J = 16.1, 10.6 Hz), 3.2 (dd, 1H, J = 5.91, 7.28 Hz), 3.08 (dd, 1H, J = 7.28, 5.91 Hz), 2.3 (m, 1H), 1.6 (m, 1H), 1.1 (s, 9H), 0.93 (d, 3H, J = 6.9 Hz), 0.82 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 143.6, 112.9, 72.3, 64.9, 39, 38.2, 27.5, 15, 13.5.

2(S*),3(S*)-Dimethyl-1-acetoxypent-4-ene (9). To a solution of **6** *anti* (200 mg, 1.17 mmol) in Et_2O (10 mL) were successively added, at room temperature, 1 mL of Ac_2O and then 30 mg of anhydrous $FeCl_3$. This solution, which turns rapidly dark brown, was stirred at room temperature, and the quantitative formation of **9** was checked by TLC (cyclohexane/EtOAc 95/5). Twenty-five mL of a saturated aqueous solution of Na_2HPO_4 was added, and the mixture was stirred for 3 h. The solid $FePO_4$ was filtered off, the aqueous layer was extracted twice with 50 mL of ether, and the organic phases were dried over $MgSO_4$ and then concentrated. The dark residue was purified by chromatography (eluent cyclohexane/AcOEt 90/10): yield 163 mg (94%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 140.9, 114.5, 67.6, 39.4, 37.2, 20.8, 17.4, 13.2.

2(S*),3(S*)-Dimethylpent-4-en-1-ol (10). To a solution of the acetate **9** (100 mg, 0.6 mmol) in MeOH (5 mL) was added at room temperature an aqueous solution of K_2CO_3 (3 M, 1 mL) and the resulting mixture heated at 40 °C for 3 h. Ten mL of Et_2O was then added, the aqueous phase was extracted twice with ether (2 × 10 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. The residue was chromatographed on SiO_2 (eluent: cyclohexane/ethyl acetate 80/ 20): yield 70 mg (88%); ^1H NMR (200 MHz, $CDCl_3$) δ 5.65 (m, 1H), 5.1 (dd, 2H, J = 18.9, 10.36 Hz), 3.65 (dd, 2H, J = 6.74, 7.47 Hz), 2.4 (m, 1H), 1.9 (s, 1H), 1.6 (m, 1H), 1.1 (d, 3H, J = 6.9, 7.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.0, 114.1, 66.3, 40.4, 39.2, 17.5, 12.8.

2(S*)-Methyl-3(R*)-methoxy-1-*tert*-butoxypent-4-ene (11 *anti*). To a solution of allyl methyl ether (0.483 mL, 5 mmol) in Et_2O (15 mL) was added 0.8 equiv of TMEDA (0.6 mL, 4 mmol), and at −70 °C 1 equiv of *s*-BuLi (1 M solution in

cyclohexane, 4 mL, 4 mmol) was slowly added. This solution was warmed at −65 °C in 1 h to complete the metalation, and then, at −65 °C, 2 equiv of $ZnBr_2$ was slowly added (1 M solution in Et_2O, 10 mL, 10 mmol) and the reaction mixture was slowly warmed to −20 °C (heterogeneous solution).

The 1(*Z*)-lithio-3-*tert*-butoxyprop-1-ene was prepared according to Bailey[21] (4 mmol, 15 mL of Et_2O) and was added to the solution of metalated allyl methyl ether. The reaction mixture was stirred at room temperature for 24 h, and the carbometalation step was followed by GC. The hydrolysis was done with a aqueous solution of HCl 1 N (2 × 10 mL), and the combined organic phases were washed with HCl 1 N (2 × 10 mL). The organic layer was treated overnight with an aqueous solution of Na_2S, washed with $NaHCO_3$ (2 × 20 mL), and then dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on SiO_2 (eluent: cyclohexane/Et_2O 98/2): yield = 520 mg (80%); ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (m, 1H), 5.25 (d, 1H, J = 9Hz), 5.20 (d, 1H, J = 18 Hz), 3.5 (4m, 1H), 3.3 (d, 1H, J = 3 Hz), 3.26 (s, 3H), 3.21 (d, 1H, J = 5 Hz), 1.9 (m, 1H), 1.17 (s, 9H), 0.87 (d, 3H, J = 7Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 118.2, 84.3, 72.3, 63.3, 56.3, 38.3, 27.6, 12.8. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.91, H 11.90. Found: C, 71.32, H, 10.78.

2(*R)-Methyl-3(*R**)-methoxy-1-*tert*-butoxypent-4-ene (11 *syn*).** The same procedure as above was used, starting with the 1(*E*)-lithio-3-*tert*-butoxyprop-1-ene: yield 525 mg (81%); ^1H NMR (400 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.2 (dd, 2H, J = 18, 8.7 Hz), 3.65 (m, 1H), 3.4 (dd, 1H, J = 5, 5.3 Hz), 3.25 (s, 3H), 3.16 (dd, 1H, J = 5, 5.3 Hz), 1.8 (m, 1H), 1.19 (s, 9H), 0.9 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 116.8, 83.2, 72.4, 63.5, 56.7, 38.9, 27.5, 11.8.

2(*S)-Methyl-3(*R**)-methoxypent-4-en-1-ol (12).** To a solution of **11** *anti* and **11** *syn* previously prepared in a 80/20 ratio (186 mg, 1 mmol) in acetonitrile (10 mL) was added *p*-toluenesulfonic acid (180 mg, 1 mmol). The solution was stirred at room temperature for 48 h. The hydrolysis was done with a solution of $NaHCO_3$ (20 mL), and 20 mL of Et_2O was then added. The aqueous phases were washed twice with Et_2O (2 × 10 mL), and the combinated organic layers were dried over Na_2CO_3. After concentration in vacuo, the residue was chromatographed on SiO_2 (eluent: CH_2Cl_2), yield 105 mg (65%, dr = 80/20). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddd, 1H, J = 18, 8.4, 10.5 Hz), 5.3 (dd, 1H, J = 1.7, 10.5 Hz), 5.21 (dd, 1H, J = 1.7, 18 Hz), 3.7 (t, 2H, J = 6.5 Hz), 3.44 (dd, 1H, J = 8.4, 8.4 Hz), 3.29 (s, 3H), 1.87 (m, 1H), 0.83 (d, 3H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 119.2, 89.3, 67.6, 56.5, 39.8, 13.7. Anal. Calcd C, 64.57; H, 10.83. Found: C, 64.17; H, 10.26.

2(*S)-Methyl-3(*R**)-methoxypent-4-en-1-oic Acid (13).** To the mixture of alcohols **12** (60 mg, 0.46 mmol, dr = 80/20) in DMF (3 mL) was added PDC (570 mg, 1.5 mmol). This solution, which rapidly turns dark, is stirred at room temperature for 3 h, and the quantitative formation of the acid was checked by TLC (eluent: CH_2Cl_2/Et_2O 50/50). Fifteen mL of a HCl 1 N solution was added, and after repetitive extraction, the organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography SiO_2 (eluent: CH_2Cl_2/Et_2O 50/50), yield 44 mg (67%, dr = 80/20). Major isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 5.60 (ddd, 1H, J = 19.0 Hz, J = 8.0, 8.0 Hz), 5.4 (m, 2H), 3.7 (t, 1H, J = 7 Hz), 3.3 (s, 3H), 2.62 (m, 1H), 1.13 (d, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178, 135.2, 120.4, 84.7, 56.6, 44.4, 13.4.

3(*S)-Methoxy-4(*R**)-[(tributylstannio)methyl]non-1-ene (14 *anti*).** To a solution of allyl methyl ether (0.483 mL, 5 mmol) in Et_2O (15 mL) was added 0.8 equiv of TMEDA (0.6 mL, 4 mmol), and at −70 °C 1 equiv of *s*-BuLi (1 M solution in cyclohexane, 4 mL, 4 mmol) was slowly added. This solution was warmed at −65 °C in 1 h to complete the metalation, and then, at −65 °C, 2 equiv of $ZnBr_2$ was slowly added (1 M solution in Et_2O, 10 mL, 10 mmol) and the reaction mixture was slowly warmed to −20 °C (heterogeneous solution).

The 1(*Z*)-lithiohept-1-ene was prepared according to Bailey[21] (4 mmol, 15 mL of Et_2O) and was added to the solution of metallated allyl methyl ether. The reaction mixture was stirred at room temperature for 24 h, the carbometalation step was followed by GC, and after quantitative formation of the bismetallic, 1 equiv of tributyltin chloride (4 mmol) was added at −30 °C. The reaction mixture was stirred for 30 min at −30 °C and warmed to 0 °C in 2 h. The hydrolysis was done with an aqueous solution of HCl 1 N (20 mL), and after usual treatment, the residue was chromatographed on SiO_2 (cyclohexane/ethyl acetate 98/2): yield 77% (1.4 g); ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddd, 1H, J = 9.35, 17.6, 7.14 Hz), 5.35 (dd, 2H, J = 18, 11 Hz), 3.5 (m, 1H), 3.4 (dd, 1H, J = 6, 11 Hz), 3.27 (s, 3H), 3.15 (dd, 1H, J = 6, 11 Hz), 1,6 (m, 6H), 1.4 (m, 11H), 1.1 (m, 8H), 0.9 (t, 12H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 118.5, 84.9, 56.5, 43.9, 32.6, 31.8, 29.6, 29.5, 28.5, 27.0, 22.6, 19.6, 15.6, 13.9, 13.5. Anal. Calcd for $C_{23}H_{48}OSn$: C, 60.14; H, 10.53. Found: C, 61.26; H, 10.91.

Reaction with the Metallated Allyl Sulfides. To a solution of allyl phenyl sulfide (0.64 mL, 4.2 mmol) in dry Et_2O (10 mL) was added TMEDA (4.85 mg, 4.2 mmol), and at −78 °C, *n*-BuLi was slowly added (1.6 M solution in hexane, 4.2 mmol). This solution was warmed to −40 °C to complete the metalation, and then, at −50 °C, $ZnBr_2$ was added (1 M solution in Et_2O, 4.2 mL, 4.2 mmol). The 2-lithio-3-*tert*-butoxyprop-1-ene was prepared as described[21] (4 mmol, 20 mL of Et_2O) and added to the solution of metalated allyl phenyl sulfide. The reaction mixture was stirred, respectively at 10 °C for 12 h and 25 °C for 24 h, and after hydrolysis and usual treatment, the corresponding products were obtained as a difficultly separable mixture of products. However, the pure cyclopropane could be isolated from the reaction mixture and **14** was isolated as a mixture of diastereoisomers, but **15** was only characterized by difference in the NMR spectrum of the crude product obtained at 10 °C.

3-(Phenylthio)-2-methyl-1-*tert*-butoxypent-4-ene (14). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.22 (m, 2H), 7.15 (m, 2H), 5.82 (ddd, 1H, J = 8, 10, 17 Hz), 4.95 (d, 1H, J = 10 Hz), 4.93 (d, 1H, J = 17 Hz), 3.8 (dd, 1H, J = 6, 8 Hz), 3.52 (dd, 1H, J = 7.5, 6.5 Hz), 3.25 (dd, 1H, J = 6.5, 7.5 Hz), 1.97 (m, 1H), 1.22 (s, 9H), 1.07 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 131.8, 128.9, 128.6, 126.5, 115.7, 72.6, 64.2, 55.7, 38.4, 27.6, 14.1.

5-(Phenylthio)-2-methyl-1-*tert*-butoxypent-4-ene (15). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (m, 5H), 6.24 (d, 1H, J_Z = 10 Hz, J_E = 15 Hz), 5.98 (dt, 1H, J_Z = 6.25, 10 Hz; J_E = 7.5, 15 Hz), 3.18 (d, 2H, J = 6 Hz), 2.22 (m, 3H), 1.18 (s, 9H), 0.91 (d, 3H, J = 7 Hz).

1-Ethenyl-2-(*tert*-butoxymethyl)cyclopropane (16). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (ddd, 1H, J = 10.4, 17, 1.6 Hz), 5.05 (dd, 1H, J = 17, 1.6 Hz), 4.82 (dd, 1H, J = 10.4, 1.6 Hz), 3.44 (dd, 1H, J = 9.4, 5.5 Hz), 3.06 (dd, 1H, J = 9.4, 5.5 Hz), 1.28 (m, 1H), 1.17 (s, 9H), 1.07 (m, 1H), 0.68 (dd, 2H, J = 6.5, 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 72.5, 64.9, 27.6, 20.4, 21.2, 12.3.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all compounds (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.