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Addition of Organometallic Compounds to Tin-Containing Cyclic Ketones. Remote Stereocontrol Induced by the Stannyl Group

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Abstract: The addition of organometallic reagents to cyclic ketones bearing stannyl groups at an appropriate distance to the carbonyl group occurs with a high level of stereocontrol, giving alcohols resulting from attack of the nucleophile syn to the tin center. This remarkable remote control is a consequence of the anchoring of the organometallic reagent by the tin and carbonyl groups. The degree of selectivity observed depends on the spatial distance between the carbonyl group and the tin center. (*Z*)-β-Stannylvinyl ketones (Sn/CO separation: 5 bonds) react with organolithium reagents, showing a high degree of stereocontrol. On the contrary, the analogous ketones with *E* stereochemistry do not show selectivity at all. In the case of β-stannyl ketones (Sn/CO separation: 3 bonds), the long distance between the tin center and the carbonyl group does not favor selective addition except when allyllithium derivatives are used. A chelation-controlled pathway assisted by the three-carbon chain of the allyl anion, which compensates the distance between tin and carbonyl groups, has been proposed. The selectivity found for ketones **34**−**36** (Sn/CO separation: 4 bonds) depends on their structure and varies with the hybridization of the carbon atom linked to the trialkyltin group. Deuterium labeling experiments as well as ab initio molecular-orbital analysis support the mechanistic hypothesis of an intramolecular delivery. Grignard reagents are less selective than organolithium compounds.

Introduction

Asymmetric synthesis by addition of a nucleophile to a carbonyl group is a fundamental reaction in organic chemistry and one of the most utilized methods for C−C bond formation in organic synthesis.[1,2] Thus, asymmetric induction from optically active substrates is a relevant and generally efficient way of inducing new chiral centers, and as such it has been extensively reviewed.[3] The most straightforward and commonly encountered example of this type of process is the addition of nonchiral nucleophiles to chiral aldehydes or ketones in which one or more new chiral centers are formed.

In past years, the search for new stereocontrolled methods on the carbonyl addition has been a major goal in organic chemistry.[1] In this sense, the asymmetric addition on a ketone adjacent to a chiral center has been largely used, but more remote inductions are less studied.[1−3]

Recently, organotin compounds were proved to be powerful intermediates in asymmetric synthesis. Thomas[4] and Nishigaichi[5] have shown the potential of the allyltin moiety in the construction of multichiral centers, reporting several examples of remote asymmetric induction using allylstannanes and carbonyl derivatives. An important area of asymmetric synthesis involving reactions of chiral allylstannanes has been thoroughly reviewed by Marshall in a recent article.[6]

In a previous communication, we reported that the addition of organometallic reagents to carbonyl groups can be sterically controlled, with a high degree of efficiency, by the presence of a β-stannylvinyl group, where the remote stannyl group (Sn/CO separation: 5 bonds) induces highly stereoselective attack from the tin-side.[7] A chelation-control mechanism was advanced to explain the remarkable stereoselectivity observed in these reactions.

This paper deals with the stereocontrolled addition of organometallic reagents to carbonyl groups induced by the presence of remote tin groups. We provide full details of the work published in preliminary form,[7] discuss the factors governing the tin-mediated stereocontrol with new examples reflecting on that problem, and report the influence of the CO/Sn separation (5, 4, or 3 bonds) on the selectivity of the organometallic addition to carbonyl groups.

(1) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vols. 1−5.
(2) Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1994.
(3) Procter, G. *Asymmetric Synthesis*; Oxford University Press: Oxford, 1996.
(4) (a) Thomas, E. J.; McNeill, A. H. *Tetrahedron lett.* **1990**, *31*, 6239. (b) Thomas, E. J.; Carey, J. S. *J. Chem. Soc., Chem. Commun.* **1994**, 283. (c) Thomas, E. J.; Carey, J. S. *Synlett* **1992**, 585. (d) Thomas, E. J.; Carey, J. S. *Tetrahedron Lett.* **1993**, *34*, 3935. (e) Thomas, E. J.; Stanway, S. J. *J. Chem. Soc., Chem. Commun.* **1994**, 285. (f) Thomas, E. J.; McNeill, A. H. *Synthesis* **1994**, 322. (g) Thomas, E. J.; Hallet, D. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2575. (h) Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1997**, 411. (i) Thomas, E. J.; Hobson, L. A.; Vincent, M. A.; Hillier, I. H. *J. Chem. Soc., Chem. Commun.* **1998**, 899.
(5) Nishigaichi, Y.; Kuramoto, M.; Takuwa, A. *Tetrahedron Lett.* **1995**, *36*, 3353; *Chem. Lett.* **1996**, 961.
(6) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(7) Barbero, A.; Cuadrado, P.; Pulido, F. J.; Rincón, J. A.; Galisteo, D.; Martínez-García, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2101.

10.1021/ja036340c CCC: $25.00

As far as we know, the long distance control promoted by the tin moiety is a striking feature, which has not been reported before, and, obviously, it could be of interest in asymmetric synthesis. The role played by the tin during the reaction pathway is also discussed throughout the text.

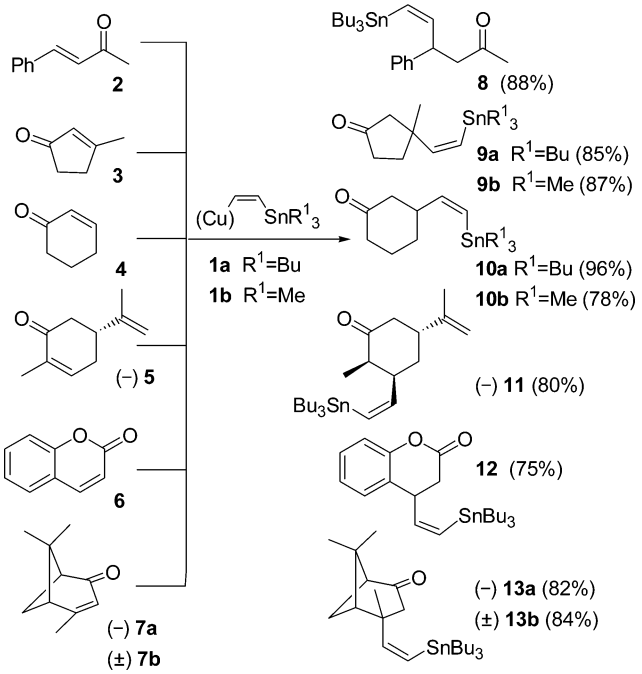
Results and Discussion

First, we considered the effect caused by the presence of a β-stannylvinyl group (CO/Sn separation: 5 bonds). Introduction of a vinylstannyl unit β to a carbonyl group was achieved following our usual stannylcupration chemistry.[8,9] During past years, the scope and synthetic applications of tin−copper addition of stannylcuprates to allenes[8] and acetylenes[9] have attracted considerable attention among chemists. Accordingly, many noticeable works regarding this area can be found in the recent literature.[10] The methodology developed has emerged as an important tool for the synthesis of allyl- and vinylstannanes.[11] Furthermore, the intermediate cuprates resulting from addition of the Cu−Sn pair to the multiple bond react with different electrophiles, leading to a large number of functionalized organic molecules containing the vinyltin moiety.[9]

(*Z*)-2-(Trialkylstannyl)vinyl cyanocuprates **1a**,**b** are readily available reagents, which can be prepared by tin-cupration of acetylenes.[9] They are synthetically equivalent to a *cis*-1,2-ethene dianion and react with a wide variety of electrophiles, giving (*Z*)-vinylstannanes with different substitution patterns.[9] In particular, linear and cyclic enones **2**−**7** undergo conjugate addition, giving (*Z*)-β-(trialkylstannyl)vinyl ketones **8**−**13** in high yield (Scheme 1). Addition of 1 equiv of BF_3 to the cuprate, before reaction with the ketone, activates[12] the cuprate, increasing the final output significantly. As it was expected, carvone **5** [(5*R*), $[\alpha]_D = -61$ (neat), Aldrich] and verbenones **7a** [(1*S*,5*S*), $[\alpha]_D = -142$ (neat), Aldrich] and **7b** (racemic) undergo highly stereoselective conjugate addition resulting from attack of the cuprate **1a** to the less hindered side of the enone to give the optically active stannylvinyl ketones **11** [(2*R*,3*R*,5*R*), $[\alpha]_D = -9.9$ ($c = 1.01$, $CHCl_3$)] and **13a** [(1*S*,4*S*,5*R*), $[\alpha]_D = -23$ ($c = 1.03$, $CHCl_3$)] and the racemic ketone **13b**, respectively. The ratio of facial diastereoselection shown by the reaction of verbenone (**7**) with cuprate **1a** seems to be very high (>99% de) because we were not able to detect the other diastereomeric ketone. In the case of carvone (**5**), besides the ketone **11** a 4% yield of the epimeric ketone at C-2 was also obtained.

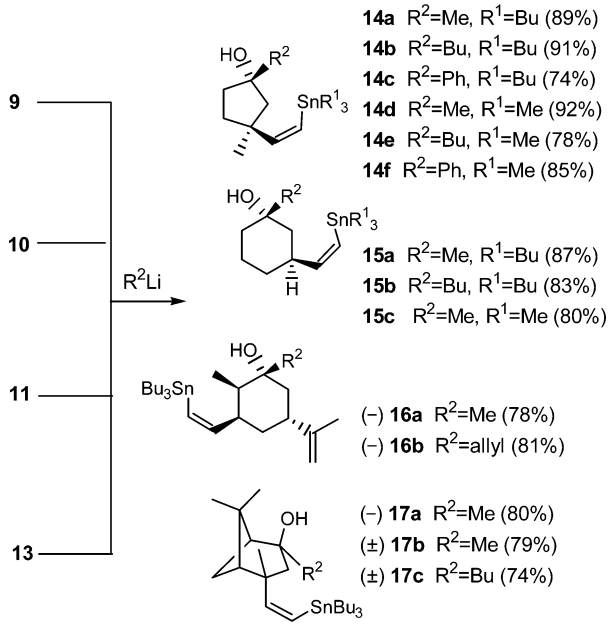
The inspection of the reaction of cyclic ketones **9**−**13** with organometallic reagents revealed the potential of the reaction.[13]

Scheme 1. Synthesis of (*Z*)-β-Vinylstannyl Ketones[a]



[a] Reaction conditions: (i) **1**, $BF_3{\cdot}Et_2O$, THF, −78 °C, 0.5 h; (ii) −78 °C to 0 °C, 1 h; (iii) NH_4Cl/H_2O, 0 °C.

Scheme 2. Addition of Organolithium Reagents to (*Z*)-β-Vinylstannylated Ketones[a]



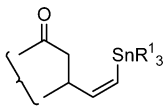
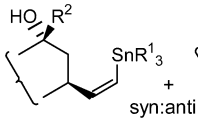
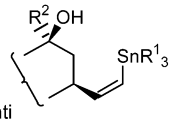
[a] Reaction conditions: (i) R^2Li (1.2 equiv), THF, −78 °C, 0.5 h; (ii) MeOH, −78 °C.

Thus, the behavior of **9**−**11** and **13** toward typical organolithium reagents shows that addition proceeds with a high level of stereoselectivity. As a result of the presence of the stannylvinyl group in the former ketones, a remarkable stereocontrolled asymmetric induction occurs on the carbonyl center. Reaction of **9**−**11** and **13** with MeLi, BuLi, PhLi, and allyllithium in THF

(8) (a) Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I.; Rowley, M. *Tetrahedron* **1989**, *45*, 413. (b) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1990**, 1030. (c) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 327. (d) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Res.* **1990**, *297*, 291.
(9) (a) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1992**, 351. (b) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1657. (c) Barbero, A.; Cuadrado, P.; García, C.; Pulido, F. J.; Rincón, J. A. *J. Org. Chem.* **1998**, *63*, 7531. See also: Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *Tetrahedron Lett.* **1992**, *33*, 5841.
(10) (a) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 770, 4993. (b) Piers, E.; Gavai, A. V. *J. Org. Chem.* **1990**, *55*, 2374, 2380. (c) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253. (d) Marino, J. P.; Edmonds, M. V.; Stengel, P. J.; Oliveira, A. R.; Simonelli, F.; Ferreira, J. T. *Tetrahedron Lett.* **1992**, *33*, 49. (e) Pereira, O. Z.; Chan, T. H. *J. Org. Chem.* **1996**, *61*, 5406.
(11) Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997.
(12) Taylor, R. J. *Organocopper Reagents: A Practical Approach*; Oxford University Press: New York, 1994.

(13) Acyclic ketones as **8** are of lesser utility, giving mixtures of diastereomeric alcohols (ca. 1:1) which are difficult to separate, whereas benzopiranone **12** leads to dirty mixtures of stannylated phenols resulting from lactone cleavage.

Table 1. Addition of Organometallic Reagents to (*Z*)-*β*-Vinylstannylated Ketones

Entry		R^2M	T (°C)	Product	 syn:anti		Yield[a] (%)
1	**9a**	MeLi	-78	**14a**	(99)	(1)	89
2	**9a**	BuLi	-78	**14b**	(99)	(1)	91
3	**9a**	PhLi	-78	**14c**	(91)	(9)	74
4	**9b**	MeLi	-90	**14d**	(99)	(1)	92
5	**9b**	BuLi	-90	**14e**	(99)	(1)	78
6	**9b**	PhLi	-90	**14f**	(89)	(11)	85
7	**9b**	CD_3Li	-90	**26**	(99)	(1)	75
8	**9a**	MeMgI	0	**14a**	(79)	(21)	96
9	**9a**	BuMgI	0	**14b**	(82)	(18)[b]	93
10	**9a**	PhMgBr	0	**14c**	(75)	(25)	82
11	**10a**	MeLi	-78	**15a**	(99)	(1)	87
12	**10a**	BuLi	-78	**15b**	(99)	(1)	83
13	**10b**	MeLi	-90	**15c**	(99)	(1)	80
14	(−) **11**	MeLi	-78	(−) **16a**	(99)	(1)	78
15	(−) **11**	allylLi	-78	(−) **16b**	(99)	(1)	81
16	(−) **13a**	MeLi	-78	(−) **17a**	(99)	(1)	80
17	(±) **13b**	MeLi	-78	(±) **17b**	(99)	(1)	79
18	(±) **13b**	BuLi	-78	(±) **17c**	(99)	(1)	74

[a] Yields refer to isolated pure compounds. [b] The anti isomer could not be well separated from the syn isomer.

at −78 °C affords diastereoselectively the tertiary alcohols **14**−**17** (Scheme 2), where the addition of the organolithium reagent takes place syn to the vinyltin moiety. The de observed with organolithiums is higher than 98% (GC-MS) except for the addition of PhLi which is not always entirely diastereoselective, leading in some experiments up to 10% of the diastereomeric alcohol with the Ph group anti to the vinyltin unit. Trimethylstannyl derivatives **9b** and **10b** require reaction temperatures near −90 °C for optimum results due to the lability of this tin group to undergo transmetalation side reactions with organolithium reagents (Scheme 2). A triphenylstannyl derivative analogue to **9** was also prepared. The synthetic usefulness of this tin group is rather limited because undesired phenyl exchange occurs to a great extent, lowering seriously the final output.

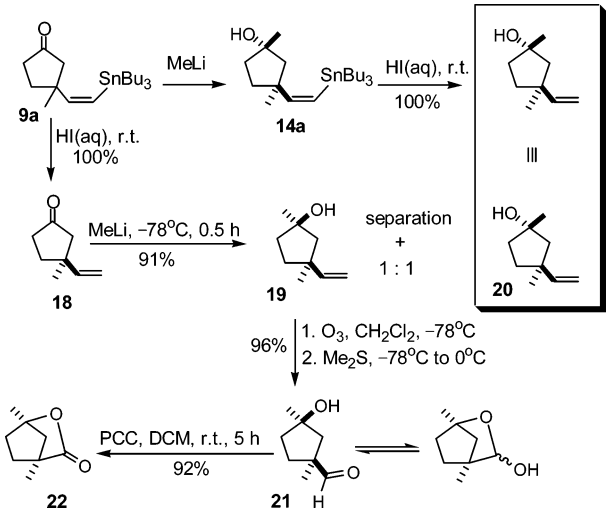
An example of how useful this remote tin-assisted effect can be in asymmetric synthesis is shown in the two-step conversion of **5** and **7a** into **16a** [(1*R*,2*R*,3*R*,5*R*), $[\alpha]_D = -29.5$ ($c = 0.4$, $CHCl_3$)], **16b** [(1*R*,2*R*,3*R*,5*R*), $[\alpha]_D = -15.3$ ($c = 0.6$, $CHCl_3$)], and **17a** [(1*S*,2*S*,4*S*,5*R*), $[\alpha]_D = -4.5$ ($c = 1.02$, $CHCl_3$)], where, starting from a chiral building block, up to three new chiral centers of defined configuration are formed with a very high degree of stereocontrol.

With organomagnesium compounds, similar results are obtained, although lower selectivities are observed (Table 1). The effect of the metal (Li or Mg) on selectivity is considered later.

Although the presence of two sterically well differentiated diastereomeric faces in bicyclic ketone **13** could explain the selective addition of the organometallic (anti to the *gem*-dimethyl group) without mediation of the tin group,[14] the high stereoselectivity observed for similar reactions in nonrigid ketones **9** and **10**, where addition of the RLi occurs exclusively from the tin side, cannot be well explained without assistance of the vinyltin group.[15] Alerted on a possible intervention of a new

(14) We think that the high de observed in the RLi additions to **13** is not entirely due to the *gem*-dimethyl group but also due to the tin-effect. In fact, destannylation of **13** (HI/THF, room temperature) followed by MeLi addition renders a lower stereoselectivity, now yielding mixtures of diastereomeric alcohols (ratio ca. 5.5:1), the major alcohol being the one with the expected syn (OH/*gem*-dimethyl) stereochemistry.

Scheme 3



kind of tin-effect, we looked for some unambiguous result such as that obtained with derivative **11**. Ab initio analysis of cyclohexanone **11** predicts equatorial positions for methyl and isopropenyl groups and an axial position for the stannylvinyl group. Coupling constants and NOE data from NMR corroborate this. Interestingly, the conformationally rigid ketone **11**, which has an axial bulky vinyltin group, also shows selective nucleophilic transfer from the side of the tin center, when equatorial attack anti to the stannylvinyl group should be favored (Scheme 2). This observation seems to be clear evidence for the participation of tin in the stereochemical course of the reaction.

Elucidation of the stereochemistry assigned to the resulting alcohols **14**−**17** was performed by both chemical (Scheme 3) and physical methods (NOE-NMR, X-ray). Thus, protodestannylation of **9a** (HI, room temperature) followed by reaction of the resulting ketone **18** with MeLi (THF, −78 °C) gives a mixture (1:1) of the diastereomeric destannylated alcohols **19** and **20** (Scheme 3). The loss of diastereoselection in the former example shows clearly the importance of the presence of the tin atom for the control of the stereochemistry of the reaction. Alcohols **19** and **20** were separated. Compound **20** is identical to a sample obtained from protodestannylation of **14a**. On the other hand, ozonolysis of **19** (O_3, CH_2Cl_2, −78 °C) followed by oxidation of the resulting hydroxyaldehyde **21** (PCC, CH_2Cl_2, 25 °C) affords the bicyclic lactone **22** (Scheme 3). Formation of **22** requires a syn relationship for the vinyl and hydroxy groups of alcohol **19**, and, hence, correlation of diastereomeric alcohol **20** with **14a** confirms the cis stereochemistry assigned for the vinyltin and 1-methyl groups of **14a**.

Structural assignment for **15b** is based on the spectral data and has been confirmed by X-ray[7] crystal structure determination of the corresponding phenylurethane (Figure 1). X-ray analysis reveals that butyl and vinyltin groups are on the same side of the molecule in a *cis*-diequatorial position.[16]

(15) It could be pointed out that torsional strain and steric factors developing in a transition state for 1,2-addition to ketones **9** and **10** would favor an equatorial (or pseudoequatorial) attack of the organolithium reagent leading to the observed stereochemistry; however, the extremely high diastereoselectivity found with organolithium compounds is not consistent with literature data. In general, for substituted cyclopentanones, poor selectivities are reported (*Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon, Elmsford, NY, 1991; Vol. 1), and even 3-*tert*-butylcyclohexanone, which probably is sterically more demanding than the 3-alkenylstannane derivative **10**, reacts with MeLi giving only a 78:22(cis:trans) ratio (Rei, M. H. *J. Org. Chem.* **1979**, *44*, 2760).

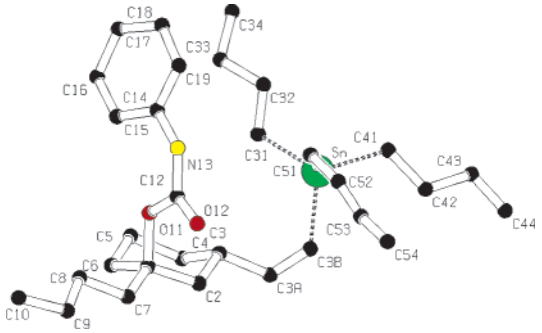
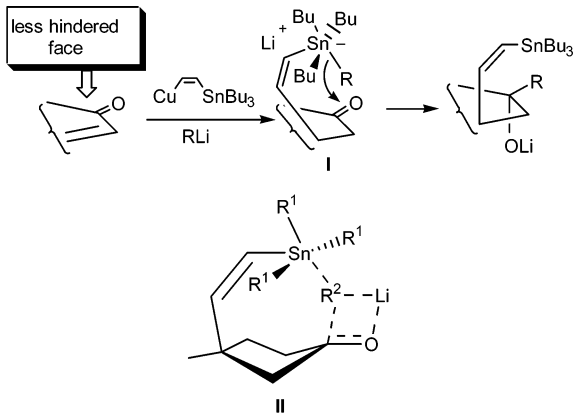
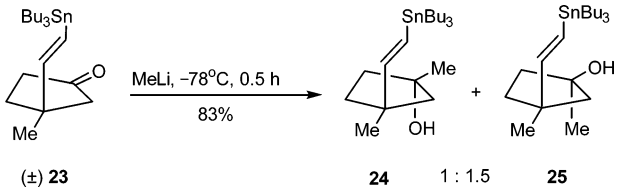


Figure 1. X-ray crystal structure of the phenylurethane derivative of **15b**.

Scheme 4



Scheme 5. Addition of Organolithium Reagents to (*E*)-*β*-Vinylstannylated Ketones



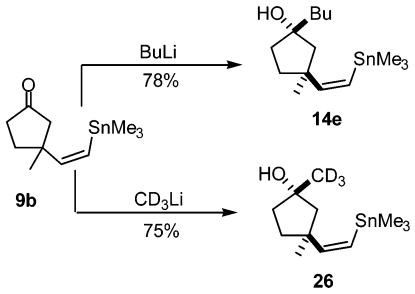
Interpretation of the observed stereoselectivity could be done if we assume that there exists a clear preference for the organometallic approaching from the tin side. Thus, the high stereocontrol observed might indicate that the reactive species is an intermediate hypervalent tin anion **I** (Scheme 4) which delivers the alkyl or Ph group by way of an intramolecular reaction. This directing effect induced by the remote tin atom has not been reported before.

According to this model, the *Z* stereochemistry of the stannylvinyl unit should play an important role over the final outcome. Effectively, we prepared the (*E*)-*β*-(tributylstannyl)-vinyl ketone **23** by using a (*E*)-2-(tributylstannyl)vinyl cyano cuprate[17] analogue to **1a**, and we found no diastereoselectivity in the reaction of **23** with MeLi, leading to an almost equimolar mixture of alcohols **24** and **25**, thus supporting the proposed model and confirming the need of a cis stereochemistry for a good control (Scheme 5).

In view of the synthetic interest of this tin-effect, we paid some attention to the mechanism of the reaction. Thus, although

(16) Crystallographic data for the structure reported have been deposited in the Cambridge Crystallographic Data Centre, ref. no. CCDC-139911. Copies of the data can be obtained from the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
(17) Corey, E. J.; Wollemberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581.

Scheme 6



the proposed intermediate **I** explains well the observed stereoselectivity, it is surprising to note the absence of scrambling reactions when the alkyl group of the organolithium compound is different from the alkyl groups attached to tin. For instance, once the butyl and R groups become mixed in intermediate **I**, one would expect that the ability for the Bu and R groups to be transferred to carbonyl was similar, and therefore mixtures should be formed if RLi ≠ BuLi. However, the only alcohol isolated is the one resulting from addition of the organolithium reagent, with no contamination of butyl alcohols. Similarly, treatment of the trimethyltin analogue **9b** with BuLi gives the 1-butylcyclopentanol (trimethyltin-derivative) **14e** as the only product (Scheme 6). Finally, we carried out a deuterium labeling experiment using ketone **9b** and deuterated MeLi. According to the former results, alcohol **26** resulting from selective addition of the deutero-methyl group from the tin side was obtained as the only product (Scheme 6). We were not able to detect scrambled methyl- and deuteriomethyl alcohols. Obviously, intermediate **I** fails to explain the lack of scrambling reactions. Apart from kinetic isotope effects, one should expect similar chemical reactivities for deuterated and nondeuterated methyl groups of the intermediate anion, and, therefore, the chemoselectivity observed is not consistent with a model as simple as the one initially proposed, even though the stereoselectivity is well explained.

It is feasible that the high diastereoselectivity found in these processes could be ascribed to some kind of chelating effect with the tin and carbonyl groups anchoring the RLi between them. Thus, results may be better rationalized if, instead of a tight complex such as **I**, we assume a chelation-control model such as **II** (Scheme 4), with the Sn−R^1 and Sn−R^2 bonds having different strength. To support theoretical evidence on this, an ab initio molecular orbital analysis of the reaction of ketone **9b** with MeLi was performed using Gaussian 98,[18] and two transition states (**TS**) for the syn- and anti-addition (related to Sn) were localized at MP2(fc)/3-21G*//HF/3-21G* theoretical levels.

The calculated structures[7] for the **TS** with a methyl anion attacking from the tin side ($\mathbf{TS_s}$) or from the opposite face ($\mathbf{TS_a}$) are given in Figure 2. Naked methyl anions were used for

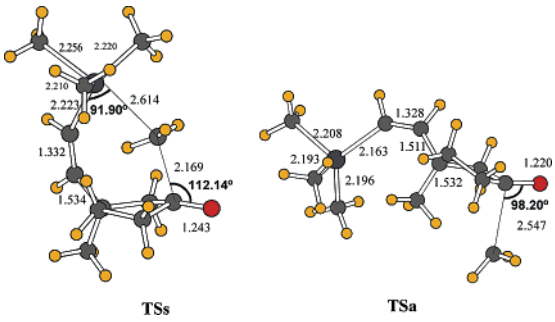


Figure 2. The calculated structures of $\mathbf{TS_s}$ and $\mathbf{TS_a}$.

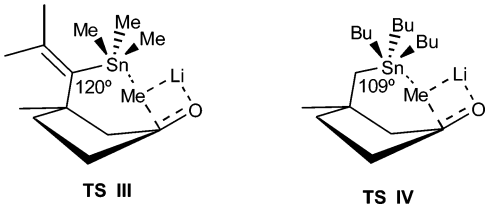


Figure 3. The transition states **III** and **IV**.

simplicity. The computed transition structure $\mathbf{TS_s}$ shows a little distorted trigonal-bipyramidal geometry at the pentacoordinate Sn atom (CH_3−Sn−C angle 91.90°). There exists a strong interaction Sn/CH_3^-/CO that is supported by the conformation of the methyl anion, which is planar, and by the length of 2.614 Å for the link Sn−C which is considerably shorter than the sum of van der Waals radii.[19] It should also be noted that the distance CO−CH_3^- in $\mathbf{TS_s}$ (2.169 Å) is shorter than that in $\mathbf{TS_a}$ (2.547 Å), which indicates that $\mathbf{TS_s}$ resembles the products more than $\mathbf{TS_a}$. The value of the CH_3−C═O angle in $\mathbf{TS_s}$ (112.14°) is closer to the tetrahedral angle than that in $\mathbf{TS_a}$ (98.20°), pointing in the same direction. Calculation of the energies for $\mathbf{TS_s}$ and $\mathbf{TS_a}$ which were estimated at the MP2(FC)/3-21G* level provides a reliable indication of the relative stability (ΔE) of the **TS**. Significantly, syn-addition is favored by 10.7 kcal mol^{-1} over the anti reaction (Figure 3). The high value of ΔE provides theoretical support for the sense of the addition observed and predicts high levels of facial diastereoselectivity, in good correlation with experimental results.

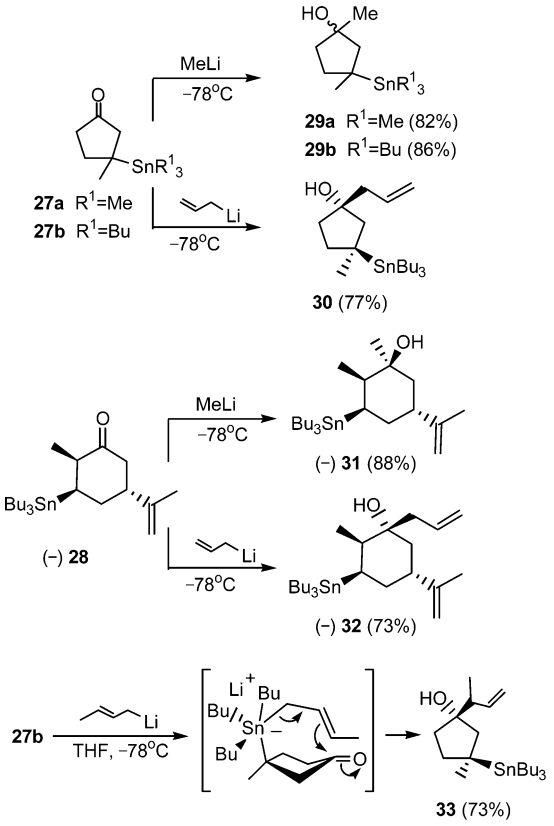
An intramolecular nucleophilic transfer was also supported by the experimental data obtained from β-stannyl ketones (CO/Sn separation: 3 bonds). The behavior of ketones **27a**,**b** and **28** (which are easily prepared by tincupration[20] of **3** and **5**) toward organolithium compounds is particularly interesting and points to the mechanistic hypothesis proposed. Thus, ketones **27a**,**b** do not show any selectivity when treated with MeLi, leading to mixtures (ratio ca. 1:1) of diastereomeric alcohols **29a**,**b**, and the conformationally rigid ketone **28** reacts with methyllithium, giving as the major product the alcohol **31**, resulting from equatorial attack (Scheme 7). However, the reaction of the same ketones with allyllithium is significant. Now, the same diastereocontrol and sense of addition is observed again, affording the alcohols **30** and **32** selectively. Moreover,

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998. Theoretical level: MP2(fc)/3-21G*//HF/3-21G*.

(19) In organotin compounds, the absence or presence of bonding to tin is often assessed by comparing the atomic separation with the sum of the r_w, where the van der Waals radius of tin is accepted to be 2.17 Å and the r_w(C) = 1.7 Å.[11]

(20) (a) Lipshutz, B. H. *Synlett* **1990**, 119. (b) Lipshutz, B. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 4617. (c) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065. (d) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78.

Scheme 7. Addition of Organolithium Reagents to β-Stannylated Ketones



addition of an asymmetrically substituted allyllithium as 2-butenyllithium[21] to the ketone **27b** seems to take place with complete allyl inversion, giving the alcohol **33** (Scheme 7). The lack of selectivity shown by ketones **27a**,**b** when MeLi is used could be due to the long spatial distance between the tin center and the carbonyl group which does not favor an intramolecular delivery. Nevertheless, the three-carbon chain of the allyl anion could compensate that distance, thus favoring the selective syn-transfer of the carbanionic moiety via a tin-ate species, as stated in Scheme 7. The allylic rearrangement observed in the reaction of **27b** with 2-butenyllithium could be a result of this anchoring effect and provides further evidence which supports the mechanistic hypothesis of an intramolecular pathway.

The results described so far show the influence of the Sn−CO bond separation on the stereocontrol of the process. To know the scope of the reaction, other tin-containing ketones with different Sn−CO distances were essayed. Effectively, anchoring effects leading to high levels of stereoselectivity were also found in the reaction of cyclic ketones **34**, **35**, and **36** (CO/Sn separation: 4 bonds) with organolithium compounds. Ketones **35** and **36** were prepared following the procedure reported by Sato.[22] Preparation of **34** is less conventional. The cuprate required for the synthesis of **34** was obtained from 1,1-bis(trimethylstannyl)isobutene[23] upon treatment with an equimolar amount of Me_2CuLi (THF, 0 °C, 30 min).

(21) (a) Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797. (b) Eisch, J. J.; King, R. B. *Organometallic Synthesis*; Elsevier: New York, 1981; Vol. 2.
(22) (a) Sato, T.; Tachibana, K.; Kawase, A.; Hirose, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3825. (b) Sato, T.; Matsuoka, H.; Igarashi, T.; Minomura, M.; Murayama, E. *J. Org. Chem.* **1988**, *53*, 1207.
(23) (a) Mitchell, T. N.; Reinmann, W. *Organometallics* **1986**, *5*, 1991. (b) Corey, E. J.; Fucchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

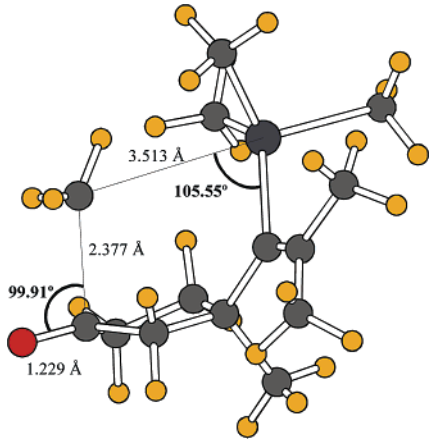
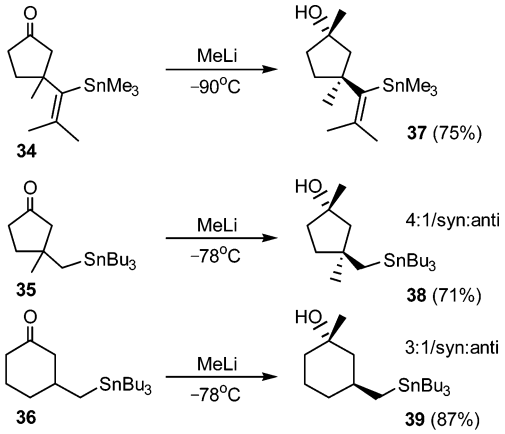


Figure 4. The calculated structure of **TS III**.

Scheme 8. Addition of Organolithium Reagents to γ-Stannylated Ketones



Reaction of **34** with MeLi (THF, −90 °C, 30 min) gives stereoselectively alcohol **37** in good yield (Scheme 8). Selective addition from the same face of the tin center is observed once more. The other diastereomeric alcohol was not found. As it was shown before, utilization of trimethylstannyl derivatives requires a lower temperature to avoid the formation of destannylated products resulting from transmetalation side reactions.

In accordance with previous examples, chelation-controlled addition (**TS III**, Figure 3) might account for the high diastereoselectivity observed for the formation of **37**.

The calculated structure for transition state **III** (Figure 4) shows a bipyramidal geometry again, with the tin atom at the center of the bipyramide, although now bond angles are slightly more distorted than before (CH_3−Sn−C angle: 105.55° in **TS III** versus 91.90° in **TS$_s$**). Transition state syn **III** was estimated to be 12.5 kcal mol^{-1} more stable than the corresponding anti state, which could explain the selectivity observed.

Reaction of **35** and **36** with MeLi (THF, −78 °C, 30 min) is less stereoselective, leading to mixtures of diastereomeric alcohols **38** and **39**, with the major addition product arising from syn attack to tin (Scheme 8). In summary, a high level of stereocontrol is still observed in stannyl ketones having a 4 bond separation between the carbonyl group and the tin center. This is very high for **34**, although an important decrease of selectivity occurs when β-stannylmethyl ketones **35** and **36** are used.

On the basis of the former results, it could be possible that the different degree of selectivity observed in these ketones

might be a consequence of the different value of the C−C−SnR_3 bond angle in transition states **III** and **IV** (nearly 120° or 109°), as it is shown in Figure 3. In fact, variation in hybridization angle could modify to some extent the relative distance Sn/CO, thus affecting the effectiveness of the anchoring effect. Although the former consideration is simply a hypothesis, not sufficiently proven, it is consistent with the fact that slight changes in structure or steric effects lead to an appreciable reduction of selectivity. In this way, the lower selectivity observed when Grignard reagents are used instead of organolithium compounds (Table 1) could be related to the change in metal size which might lead to a less favorable transition state. However it may be, more theoretical work is probably needed before a definitive assertion could be done.

In conclusion, this paper reports the unexpected and novel observation that a trialkyltin substituent can deliver an alkyllithium reagent stereoselectively to the proximal face of a neighboring ketone. Experimental and theoretical data are in good agreement with the intramolecular nucleophile transfer that is put forward. The absence of selectivity observed with (*E*)-vinylstannanes helps to substantiate the mechanistic hypothesis. On the other hand, deuterium labeling experiments point to a chelation-controlled addition which is also supported by ab initio analysis. The stereoselectivity diminishes as the distance Sn/CO varies from 5 to 3 bonds. The total loss of selectivity found in *β*-stannyl ketones (3 bonds separation) can be associated with the long spatial distance between the tin center and the carbonyl group; however, allyllithiums compensate that distance leading to highly stereoselective reactions, which supports the anchoring effect proposed.

Experimental Section

^{1}H and ^{13}C NMR experiments were taken at 300 and 75 MHz, respectively. Ab initio analyses were performed on a Silicon Graphics O2 R5000SC workstation using the Gaussian 98 program. The stereochemistry of the compounds has been assigned on the basis of NOE and NOESY experiments.

Conjugate Addition of Stannylvinylcuprates to Enones: General Procedure. BF_3·Et_2O (1.1 mL, 1.250 g, 8.8 mmol) was added dropwise to a solution of 4.4 mmol of the *cis*-stannylvinylcuprates[9b,20b,c,24] **1a**,**b** at −78 °C. The resulting mixture was stirred at this temperature for 5 min, and then a solution of the corresponding enones **2**−**7** (4 mmol) in 2 mL of THF was slowly added through syringe. The well-stirred mixture was kept at −78 °C for 30 min, and then warmed to 0 °C over 1 h and quenched with 2 mL of CH_3OH. The reaction mixture was warmed to room temperature, diluted with 20 mL of Et_2O, and washed thoroughly with 30 mL of NH_4Cl sat./NH_4OH (10%) solution. The aqueous layer was extracted with diethyl ether (2 × 25 mL), the combined organic fractions were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was chromatographed under appropriate conditions to afford the corresponding conjugate addition products **8**−**13** in high yields.

3-Methyl-3-((*Z*)-2-tributylstannylvinyl)cyclopentan-1-one (9a). Yellow pale oil (85%). IR (film): 1730, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.75 (d, $^3J_{Sn-H}$ = 160 Hz, J = 15 Hz, 1H), 5.70 (d, $^2J_{Sn-H}$ = 60 Hz, J = 15 Hz, 1H), 2.33 (d, J = 20 Hz, 1H), 2.33 (t, J = 8 Hz, 2H), 2.1 (d, J = 20 Hz, 1H), 2.0 (m, 1H), 1.85 (m, 1H), 1.5−0.8 (m, 27H, Bu_3Sn), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 219.1, 156.2, 125.8, 52.2, 44.1, 37.3, 36.5, 29.4, 27.3, 26.1, 14.1, 11.2. MS (EI) *m*/*z* 357 (M^+ − Bu, 48%), 121 (54%). HRMS (EI) calcd for [$C_{20}H_{37}OSn$] ([M − H]$^+$) 413.1866, found 413.1867.

[2*R*,3*R*,5*R*]-5-Isopropenyl-2-methyl-3-((*Z*)-2-tributylstannylvinyl)-cyclohexan-1-one (11). Yellow pale oil (80%). IR (film): 1700, 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.29 (dd, $^3J_{Sn-H}$ = 143 Hz, J = 12.4, 9.7 Hz, 1H), 5.97 (d, $^2J_{Sn-H}$ = 67 Hz, J = 12.4 Hz, 1H), 4.8 (s, 1H), 4.75 (s, 1H), 2.7−2.6 (m, 3H), 2.5 (ddd, J = 13.1, 4.1, 1.9 Hz, 1H), 2.3 (t, J = 13.1 Hz, 1H), 1.95 (td, J = 13.1, 3.7 Hz, 1H), 1.85 (m, 1H), 1.73 (s, 3H), 1.5−0.8 (m, 27H, Bu_3Sn), 0.94 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 212.1, 147.5, 146.8, 132.1, 109.2, 49.5, 47.5, 46.5, 41.3, 38.2, 29.2, 27.3, 20.1, 13.6, 12.5, 10.2. MS (EI) *m*/*z* 411 (M^+ − Bu, 42%), 41 (100%). $[\alpha]^{25}_D$ −9.9 (*c* 1.0, $HCCl_3$). Anal. Calcd for $C_{24}H_{44}$-OSn: C, 61.69; H, 9.49. Found: C, 61.83; H, 9.60. NOE enhancements were found between the following signals: (a) 1.73 (Me−C═) to 2.3 (C_6-H_{ax}), (b) 2.5 (C_6-H_{ec}) to 0.94 (C_2−Me), (c) 0.94 (C_2−Me) to 1.5−1.2 ($SnBu_3$).

Addition of Organolithium Reagents to Stannylated Ketones: General Procedure. A solution of 1 mmol of the stannylated ketone in 3 mL of THF was cooled at −78 °C or −90 °C (depending on the substrate used: tributyltin or trimethyltin derivatives). The corresponding organolithium reagent (1.1 mmol) was slowly added dropwise and stirred for 30 min at the same temperature. The reaction was quenched with 0.5 mL of CH_3OH and warmed to room temperature. The mixture was diluted with 5 mL of diethyl ether and washed successively with a saturated solution of NH_4Cl (2 mL) and brine (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was chromatographed in silica gel, under appropriate conditions, to afford the corresponding stannylated alcohols in high yields.

[1*S,3*S**]-1,3-Dimethyl-3-(*cis*-2-tributylstannylvinyl)cyclopentan-1-ol (14a).** Yellow pale oil (89%). IR (film): 3620, 3360, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.74 (d, $^3J_{Sn-H}$ = 175 Hz, J = 14 Hz, 1H), 5.62 (d, $^2J_{Sn-H}$ = 75 Hz, J = 14 Hz, 1H), 1.85 (d, J = 14 Hz, 1H), 1.82−1.7 (m, 4H), 1.65 (d, J = 14 Hz, 1H), 1.5−0.9 (m, 27H, Bu_3Sn), 1.40 (br s, −O*H*), 1.35 (s, 3H), 1.22 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.1, 123.3, 80.1, 55.0, 46.3, 41.2, 40.5, 29.8, 29.1, 28.5, 27.3, 14.0, 11.2. MS (EI) *m*/*z* 373 (M^+ − Bu, 62%), 43 (100%). Anal. Calcd for $C_{21}H_{42}OSn$: C, 58.76; H, 9.86. Found: C, 58.97; H, 10.02.

[1*S,3*S**]-1-Butyl-3-((*Z*)-2-tributylstannylvinyl))cyclohexan-1-ol (15b).** Liquid (83%). IR (film): 3600, 3500, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.27 (dd, $^3J_{Sn-H}$ = 140 Hz, J = 12, 10 Hz, 1H), 5.70 (d, $^2J_{Sn-H}$ = 70 Hz, J = 12 Hz, 1H), 2.2 (m, 1H), 1.6−0.8 (m, 45H, Bu, 4C*H*$_2$, Bu_3Sn, OH). ^{13}C NMR ($CDCl_3$): δ 154.3, 126.1, 70.9, 44.4, 43.5, 41.7, 36.0, 32.7, 29.2, 27.3, 25.1, 23.2, 21.0, 13.9, 13.7, 10.3. MS (EI) *m*/*z* 415 (M^+ − Bu, 5%), 397 (M^+ − Bu − H_2O, 39%), 41 (100%). Anal. Calcd for $C_{24}H_{48}OSn$: C, 61.16; H, 10.26. Found: C, 61.39; H, 10.41.

[1*R*,2*R*,3*R*,5*R*]-1-Allyl-2-methyl-5-isopropenyl-3-((*Z*)-2-tributylstannylvinyl)cyclohexan-1-ol (16b). Yellow pale oil (81%). IR (film): 3490, 1640, cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.14 (dd, $^3J_{Sn-H}$ = 141 Hz, J = 12.0, 10.0 Hz, 1H), 5.83 (d, $^2J_{Sn-H}$ = 67 Hz, J = 12.0 Hz, 1H), 5.82 (ddt, J = 16.5, 10.5, 7.4 Hz, 1H), 5.14 (d, J = 10.5 Hz, 1H), 5.11 (d, J = 16.5 Hz, 1H), 4.70 (s, 1H), 4.69 (s, 1H), 2.53 (tt, J = 12.6, 2.7 Hz, 1H), 2.27 (d, J = 7.4 Hz, 2H), 2.24−2.16 (m, 1H), 1.76−1.67 (m, 2H), 1.73 (s, 3H), 1.62−0.80 (m, 34H, C*H*, C*H*$_2$, C*H*$_3$, −O*H*, Bu_3Sn). ^{13}C NMR ($CDCl_3$): δ 151.6, 150.2, 133.7, 128.7, 118.6, 108.4, 74.1, 48.8, 46.7, 42.5, 39.5, 38.9, 34.9, 29.2, 27.3, 21.0, 13.6, 13.2, 10.3. MS (EI) *m*/*z* 411 (M^+ − Bu − C_3H_6), 41 (100%). $[\alpha]^{25}_D$ −15.3 (*c* 0.60, $HCCl_3$). Anal. Calcd for $C_{27}H_{50}OSn$: C, 63.66; H, 9.89. Found: C, 63.98; H, 10.09. NOESY enhancements were found between the following signals: (a) 2.27 (CH_2−C═) to 0.95−0.8 ($SnBu_3$), (b) 2.53 (C_5-H_{ax}) to 7.14 (−CH═CSn).

[1*S,3*S**]-1,3-Dimethyl-3-((*E*)-2-tributylstannylvinyl)cyclopentan-1-ol (24).** Yellow pale oil (33%). IR (film): 3400, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.98 (d, $^3J_{Sn-H}$ = 70 Hz, J = 20 Hz, 1H), 5.80 (d, $^2J_{Sn-H}$ = 80 Hz, J = 20 Hz, 1H), 1.9 (d, J = 14 Hz, 1H), 1.73 (m, 4H), 1.6

(24) (a) Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, *31*, 165. (b) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(d, $J = 14$ Hz, 1H), 1.5−0.9 (m, 28 H, 1H and Bu_3Sn), 1.35 (s, 3H), 1.20 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.2, 120.1, 81.2, 53.8, 47.9, 42.4, 39.3, 30.1, 29.5, 28.2, 27.4, 13.9, 10.2. MS (EI) *m*/*z* 373 ($M^+ - Bu$, 100%).

[1*R,3*S**]-1,3-Dimethyl-3-((*E*)-2-tributylstannylvinyl)cyclopentan-1-ol (25).** Yellow pale oil (50%). IR (film): 3400, 1590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.25 (d, $^3J_{Sn-H} = 64$ Hz, $J = 20$ Hz, 1H), 5.94 (d, $^2J_{Sn-H} = 76$ Hz, $J = 20$ Hz, 1H), 2.03 (d, $J = 20$ Hz, 1H), 1.98 (t, $J = 8$ Hz, 2H), 1.88 (d, $J = 20$ Hz, 1H), 1.88 (m, 2H), 1.5−0.9 (m, 27H, Bu_3Sn), 1.34 (s, 3H), 1.26 (br s, −OH), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.2, 120.8, 81.1, 55.4, 47.3, 41.9, 38.2, 30.1, 29.4, 27.7, 27.2, 13.7, 10.1. MS (EI) *m*/*z* 355 ($M^+ - Bu - H_2O$, 100%). Anal. Calcd for $C_{21}H_{42}OSn$: C, 58.76; H, 9.86. Found: C, 59.03; H, 9.99.

[1*S,3*S**]-3-Methyl-1-trideuteriomethyl-3-((*Z*)-2-trimethylstannylvinyl)cyclopentan-1-ol (26) (Prepared at −90 °C).** Yellow pale oil (75%). ^1H NMR ($CDCl_3$): δ 6.71 (d, $^3J_{Sn-H} = 170$ Hz, $J = 13.7$ Hz, 1H), 5.81 (d, $^2J_{Sn-H} = 70$ Hz, $J = 13.7$ Hz, 1H), 1.87 (d, $J = 13.6$ Hz, 1H), 1.76 (m, 4H), 1.67 (d, $J = 13.6$ Hz, 1H), 1.45 (s, −OH), 1.23 (s, 3H), 0.30 (s, $^2J_{Sn-H} = 55$ Hz, 9H, Me_3Sn). ^{13}C NMR ($CDCl_3$): δ 160.1, 125.2, 79.9, 55.2, 46.8, 41.2, 40.0, 30.2, −7.1. MS (EI) *m*/*z* 292 ($M^+ - CH_3$, 49%), 46 (100%).

[1*S,3*S**]-1-(1-Methylallyl)-3-methyl-3-tributylstannylcyclopentan-1-ol (33).** Yellow pale oil (73%). IR (film): 3420, 1640, cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.85 (ddd, $J = 15.3$, 11.8, 7.5 Hz, 1H), 5.10 (d, $J = 11.8$ Hz, 1H), 5.08 (d, $J = 15.3$ Hz, 1H), 2.22 (dq, $J = 7.5$, 6.9 Hz, 1H), 2.02 (dd, $J = 14.2$, 10.9 Hz, 1H), 1.59 (s, −OH), 1.36 (s, 3H), 1.06 (d, $J = 6.9$ Hz, 3H), 1.95−1.67 (m, 5H), 1.6−0.7 (m, 27H, Bu_3Sn). ^{13}C NMR ($CDCl_3$): δ 140.5, 115.7, 84.3, 51.6, 50.7, 47.7, 39.2, 31.3, 29.3, 27.6, 29.2, 14.7, 13.6, 8.3 (some signals show doublets corresponding to the epimeric allylic CH protons). MS (EI) *m*/*z* 387 ($M^+ - Bu$, 10%), 55 (100%). Anal. Calcd for $C_{22}H_{44}OSn$: C, 59.61; H, 10.00. Found: C, 59.93; H, 10.26.

[1*S,3*S**]-1,3-Dimethyl-3-(2-methyl-1-trimethylstannyl-1-propenyl)cyclopentan-1ol (37) (Prepared at −90 °C).** Amorphous solid (75%). ^1H NMR ($CDCl_3$): δ 2.0 (d, $J = 13.6$ Hz, 1H), 1.90 (d, $J = 13.6$ Hz, 1H), 1.85−1.7 (m, 4H), 1.77 (2s, 6H), 1.35 (s, 1H, OH), 1.30 (s, 3H), 1.25 (s, 3H), 0.20 (s, $^3J_{Sn-H} = 50$ Hz, 9H, Me_3Sn). ^{13}C NMR ($CDCl_3$): δ 151.1, 139.2, 79.8, 58.1, 50.2, 43.2, 41.7, 41.1, 29.8, 28.8, 24.9, −4.0. MS (EI) *m*/*z* 317 ($M^+ - CH_3$, 61%), 135 (100%). Anal. Calcd for $C_{14}H_{28}OSn$: C, 50.79; H, 8.52. Found: C, 51.02; H, 8.73.

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Supporting Information Available: Experimental procedures and product characterization for ketones **27a**,**b**, **28**, **34**−**36**; characterization of ketones **8**, **9b**, **10a**,**b**, **12**, **13**, **23**; characterization of alcohols **14a**,**c**−**f**, **15a**,**c**, **16a**, **17**, **29**−**32**, **38**, and **39**; experimental procedures and product characterization for compounds **18**−**22**; X-ray crystallographic data for phenylurethane of **15b**; data for ab initio calculations of $\mathbf{TS_a}$, $\mathbf{TS_s}$, and **TS III** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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