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Remote Stereocontrol in Carbonyl Additions Promoted by Vinylstannanes**

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The search for highly stereocontrolled routes for the preparation of chiral compounds is an important goal in organic chemistry.[1, 2] The asymmetric addition of nucleophiles to carbonyl groups is a cornerstone of organic synthesis and as such has been extensively reviewed.[3] Although asymmetric induction by stereogenic centers adjacent to carbonyl groups has been widely studied, more remote inductions are less well known.[1–3]

Thomas and co-workers reported the potential of the allylstannane moiety in the construction of chiral compounds, and showed many examples of remote asymmetric induction by allylic tin reagents and oxocompounds.[4] Other outstanding reactions that involve chiral allylstannanes were reviewed by Marshall.[5]

Herein we report a highly efficient stereocontrolled addition of organometallic reagents to carbonyl groups in the presence of a (*Z*)-β-stannylvinyl group. The remote stannyl group induces a highly stereoselective attack from the same face on which the tin center is found. To the best of our knowledge, the long-distance control effected by the vinyltin moiety has not been observed before. The role of the tin center, the influence of the Sn–CO bond separation, and a hypothetical mechanistic pathway that leads to this remarkable stereocontrol are discussed herein.

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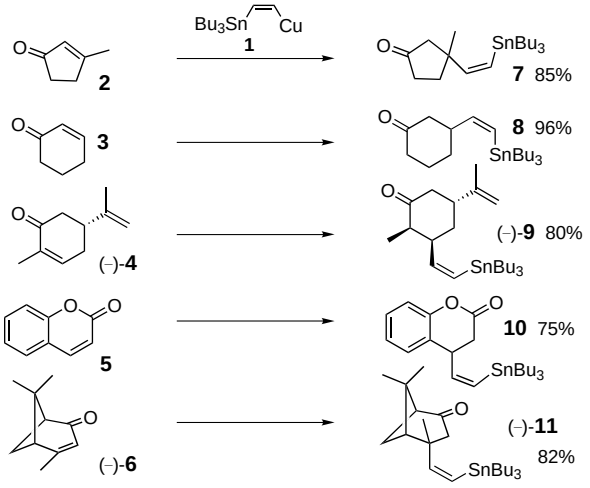
The introduction of a vinylstannyl unit β to a carbonyl group was achieved by stannylcupration of acetylene, followed by treatment with α,β-unsaturated ketones. The stannylcupration of allenes[6] and acetylenes[7] has emerged as an important tool in the synthesis of allyl- and vinylstannanes.[8, 9]

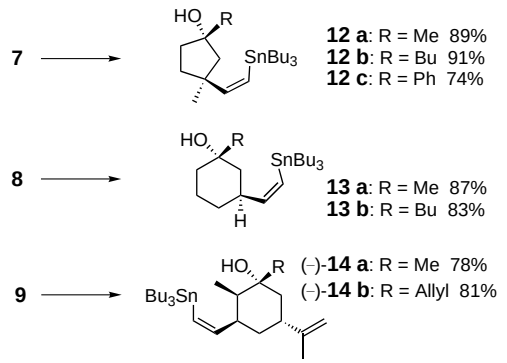
cis-2-(Tributylstannyl)vinyl cyanocuprates **1**[7] react with enones **2** – **6** to give, after conjugate addition, *cis*-β-(tributylstannyl)vinyl ketones **7** – **11** in good yield (Scheme 1). The



Scheme 1. Reaction of enones **2** – **6** with cuprate **1**. Reagents and conditions: 1) **1** (1.0 equivalent), $BF_3 \cdot Et_2O$, THF, $-78\,^{\circ}C$, 30 min; 2) $-78 \rightarrow 0\,^{\circ}C$, 1 h; 3) NH_4Cl/H_2O, $0\,^{\circ}C$.

addition of one to two equivalents of BF_3 to the cuprate prior to the addition to the ketone increases the final yield significantly.[10] (–)-(5*R*)-Carvone (**4**) and (–)-(1*S*,5*S*)-verbenone (**6**) underwent stereoselective conjugate addition to give the optically active ketones (2*R*,3*R*,5*R*)-**9** and (1*S*,4*S*,5*R*)-**11**, respectively.[11a]

The behavior of **7** – **9** toward typical organolithium reagents shows that addition occurs with a high degree of stereocontrol. The reaction of **7** – **9** with MeLi, BuLi, allyllithium, and PhLi in THF at $-78\,^{\circ}C$ affords diastereoselectively the tertiary alcohols **12** – **14** (Scheme 2), respectively, in which the addition of the alkyl or phenyl groups takes place *syn* to the



Scheme 2. Stereoselective addition of organolithium reagents to β-stannylvinyl ketones **7**, **8**, and **9**. Reagents and conditions: 1) RLi (1.2 equivalents), THF, $-78\,^{\circ}C$, 30 min; 2) MeOH, $-78\,^{\circ}C$.

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vinyltin moiety. The *de* values in all the studied examples is greater than 98% (GC-MS), except for the addition of PhLi which in some experiments also gave up to 10% of the other diastereomer.

An indication of how this reaction might be applied to asymmetric synthesis is shown in the successive conversion of **4**→**9**→**14a**[11b], in which new stereogenic centers of defined configuration are formed consecutively, starting from a chiral building block.

The stereochemistry assigned to the resulting alcohols **12**–**14** was confirmed by both physical (NOE, X-ray) and chemical[12] methods. X-ray analysis of the phenylurethane derivative of **13b** (Figure 1) reveals that the butyl and the vinyltin groups are on the same side of the molecule in a *cis* diequatorial arrangement.[13]

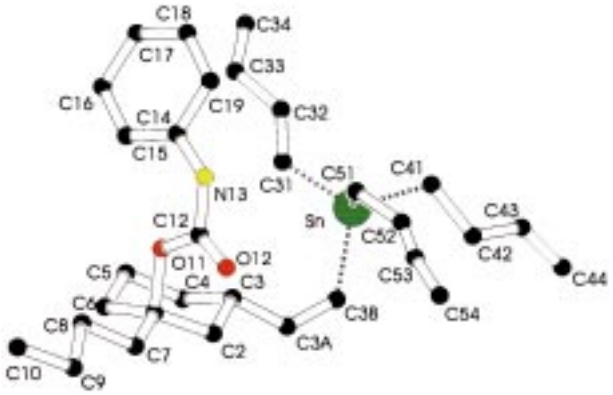
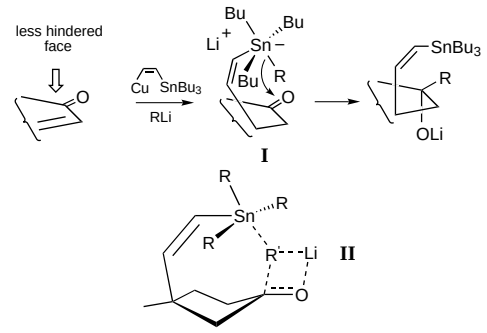


Figure 1. X-ray crystal structure of the phenylurethane derivative of **13b**.

Although the stereoselectivity observed in the reactions of ketones **7** and **8** could be explained without the mediation of the tin group, the diastereocontrol associated with ketone **9**, in which addition occurs from the same face as the tin center, cannot be easily explained without the assistance of the vinyltin group. Thus, in the case of ketones **7** and **8**, torsional strain and steric factors may lead to the observed high levels of stereocontrol.[14] However, the conformationally rigid ketone **9**, which has the bulky stannylvinyl group in the an axial position,[15] also shows selective nucleophilic transfer from the face on which the tin center is found, when equatorial attack *anti* to the stannylvinyl group should be favored. This latter observation could be evidence for the participation of tin in the stereochemical course of the reaction.

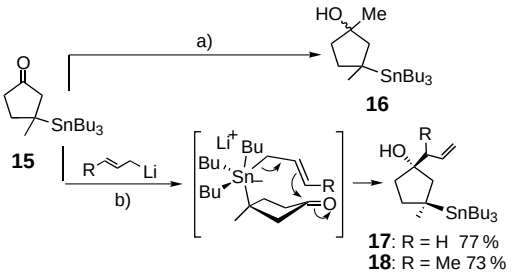
The stereoselectivity of these reactions could be interpreted if we assume that there exists a clear preference for the organometallic group to approach from the face on which the tin group is found. The high stereocontrol observed might then indicate that the reactive species is an intermediate pentacovalent stannate anion **I** (Scheme 3), which delivers the alkyl or phenyl group by means of an intramolecular reaction. The *Z* stereochemistry of the stannylvinyl unit could favor the proposed intramolecular nucleophilic transfer. This directing effect, which is promoted by the remote tin center, has not been reported before.

The reaction of ketone **15** (readily available from stannylcupration of **2**) with organolithium reagents is significant.



Scheme 3. Directing effect of the stannate moiety in the proposed mechanism.

Compound **15** does not show any selectivity toward the attack of methyllithium and gives an almost equimolar mixture of diastereomeric alcohols **16** (Scheme 4). However, when



Scheme 4. Reaction of ketone **15** with organolithium compounds. Reagents and conditions: a) MeLi, THF, −78 °C, 86%; b) THF, −78 °C.

allyllithium is used, the same selectivity and mode of addition is observed again, affording the alcohol **17**. Moreover, the reaction of **15** with 2-butenyllithium takes place apparently with complete allyl inversion to give **18** (Scheme 4). The lack of selectivity in the reaction of **15** with MeLi could be a result of the long spatial distance between the tin center and the carbonyl groups which does not favor intramolecular delivery. On the contrary, the three-carbon chain of the allyl or butenyl group could compensate for that distance, thus favoring the selective addition *syn* to the tin center. The allylic rearrangement supports this hypothesis of an intramolecular pathway (Scheme 4).

Although the proposed intermediate **I** explains the observed stereoselectivity well, the absence of scrambling reactions when the organolithium reagent is not BuLi is surprising. Similarly, treatment of the trimethyltin analogue **19**[7] with BuLi gives the 1-butylalcohol (trimethyltin derivative) **20** as the only product (Scheme 5). Moreover, reaction of ketone **19** with deuterated MeLi leads to the alcohol **21**, which results from the selective addition of the deuteromethyl group from the same face as the tin center (Scheme 5). We were not able to detect scrambled methyl- and deuteromethylalcohols. Evidently, intermediate **I** fails to explain the lack of scrambling. Also, the chemoselectivity observed in the deuterium-labeling experiment is not consistent with a model as simple as the one initially proposed.

It is feasible that the high diastereoselectivity found in these processes could be ascribed to some kind of chelating effect

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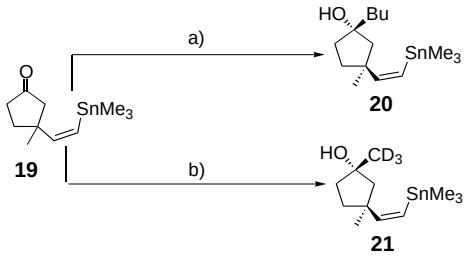

Scheme 5. Reagents and conditions: a) BuLi, THF, $-90\,^{\circ}C$, 30 min, 78%; b) CD_3Li (1.2 equivalents), THF, $-90\,^{\circ}C$, 30 min, 75%.

with the tin and carbonyl groups anchoring the RLi in between them. The results may be better rationalized if instead of a tight complex such as **I**, we assume a chelation-control model such as **II** (Scheme 3), in which the Sn–R and Sn–R^1 bonds have different strengths. The allyl inversion observed in **18** could thus arise from this anchoring effect.

To support theoretical evidence of the proposed mechanism, an ab initio molecular-orbital analysis of the reaction of ketone **19** with MeLi was performed by using Gaussian 98,[16] and two transition states (TS_s and TS_a) for the *syn* and *anti* addition (relative to Sn) were localized (Figure 2). The energies for the transition states when a methyl anion approaches **19** were estimated and it was found that *syn* addition is favored over the *anti* reaction by 10.7 kcal mol^{-1}.

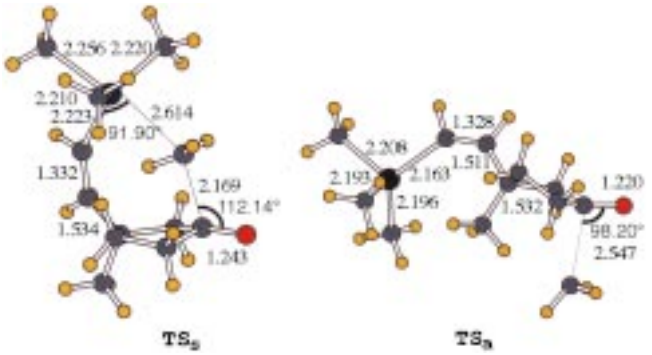

Figure 2. The calculated structures of TS_s and TS_a.

Work in progress shows that high levels of stereocontrol are also obtained when Grignard reagents are used instead of organolithium compounds.

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[11] a) (–)-(5*R*)-Carvone: $[\alpha]_D = -61$ (neat), Aldrich; (–)-(1*S*,5*S*)-verbenone: $[\alpha]_D = -142$ (neat), Aldrich; 2*R*,3*R*,5*R*-**9**: $[\alpha]_D = -9.9$ ($c = 1.01$, $CHCl_3$)—a 4% yield of the C-2 epimeric ketone was also isolated; 1*S*,4*S*,5*R*-**11**: $[\alpha]_D = -23$ ($c = 1.03$, $CHCl_3$); b) (1*R*,2*R*,3*R*,5*R*)-**14a**: $[\alpha]_D = -29.5$ ($c = 0.4$, $CHCl_3$).
[12] Chemical confirmation of the stereochemistry assigned to **12a** was obtained as follows: a diastereomeric mixture of 1,3-dimethyl-3-vinylcyclopentan-1-ol was obtained by adding lithium divinyl cuprate to **2**, and reacting the resulting ketone with MeLi. The two diastereomeric cyclopentanol compounds were separated: the 1-methyl/3-vinyl *syn* cyclopentanol is identical to that obtained from protodestannylation (HI/THF) of **12a**, whereas the other cyclopentanol (1-methyl/3-vinyl *anti*) was converted into the bicyclic lactone 1,4-dimethyl-3-oxa-bicyclo[2,2,1]heptan-2-one by ozonolysis followed by oxidation (PCC/CH_2Cl_2) of the resulting hydroxyaldehyde.
[13] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-139911. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[14] The pseudo-axial position of the methyl group in ketone **7** should favor the attack of the organometallic reagent from the less hindered side, *anti* to the methyl group and hence *syn* to vinyltin group. Similarly, for the ketone **8**, equatorial attack would be favored which could explain the diastereoselectivity observed.
[15] Ab initio analysis of cyclohexanone **9** predicts equatorial positions for methyl and isopropenyl groups and an axial position for the stannylvinyl group. Coupling constants and NOE data from NMR spectroscopic analysis corroborate this.
[16] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**. Theoretical level: MP2(fc)/3-21G*//HF/3-21G*. Naked methyl anions were used for simplicity.

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