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1-Alkoxyallene as an Effective Precursor for Regio- and Stereocontrolled Allylation Reactions with Aliphatic Aldehydes via Bis-Stannylation

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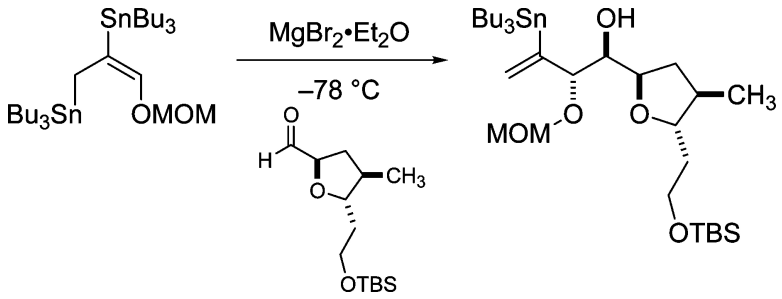

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1-Alkoxyallene as an Effective Precursor for Regio- and Stereocontrolled Allylation Reactions with Aliphatic Aldehydes via Bis-Stannylation

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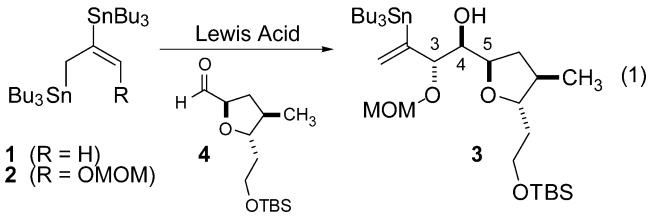
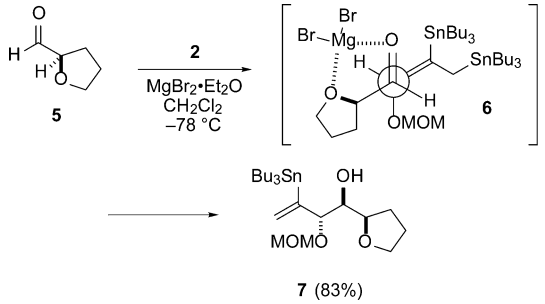
Previous studies in these laboratories have developed a strategy to utilize stereocontrolled allylation reactions in tandem with Pd-catalyzed couplings to efficiently prepare complex dienes as exemplified in amphidinolide K.[1] These studies were facilitated by the quantitative and facile bis-stannylation of allene[2] and the convenient use of **1** in asymmetric allylations.[3] Similarly, recent reports have featured advances for the analogous Pd-catalyzed diboration of allenes.[4,5] In addition, the hydroboration of allenylboronates has provided for regiocontrolled 1,3-bifunctionalization of the allyl unit and for sequential condensations with aldehydes.[6] To address key issues of convergency in an ongoing natural product synthesis, we required the assembly of three contiguous stereogenic carbons, as illustrated in **3** (eq 1), each with differentiated oxygen substitution, and the feasibility for subsequent Stille coupling. In this report, we describe the bis-stannylation of 1-alkoxyallenes and the use of fully functionalized (*E*)-(3-(methoxymethoxy)prop-2-ene-1,2-diyl) bis-tributylstannane (**2**) for a study of stereocontrolled allylation reactions with aldehydes.



Early developments concerning the bis-stannylation of 1-methoxyallene described product mixtures which are derived from kinetic and thermodynamic processes.[7] Tius and co-workers have reported the preparation and utility of 1-(methoxy)methoxyallene for significant advances of the Nazarov cyclopentannelation.[8] This allene proved to be a worthy point of departure for our studies as reactions with neat hexabutylditin at 95 °C in the presence of tetrakis-(triphenylphosphine)palladium catalyst yielded **2** (88%) as a single olefin isomer.

Functionalized 2-propenylstannane **2** is highly reactive with a variety of aliphatic aldehydes, as highlighted by stereoselective formation of alcohol **3** (57%) as a single diastereomer bearing the 3,4-*anti*-4,5-*syn*-relationship. Reactions with nonracemic **4** have been conducted in CH_2Cl_2 at −78 °C using a slight excess of stannane **2** (1.5 equiv) followed by the addition of $MgBr_2$ etherate (2 equiv). To avoid side product arising from destannylation of product **3**, 2,6-di-*tert*-butyl-4-methylpyridine is introduced prior to the Lewis acid, and reactions are quenched with aqueous $NaHCO_3$.

A survey of reactions with aliphatic aldehydes is summarized in Table 1. The added presence of the pyridine base permits reaction temperatures of −40 to 0 °C without destannylation. However, this acid-catalyzed decomposition was generally avoided by maintaining reactions at −78 °C. As exemplified by the formation of **3** (eq 1), chiral α-alkoxyaldehydes (entries 1−6, Table 1) provided excellent yields with high stereoselectivity using magnesium bromide etherate. In many cases, only a single diastereomer could be observed by NMR analyses of crude reaction product. A mechanistic rationale featuring a chelation-controlled addition as described for **5** illustrates a synclinal S_E2' reaction via the open transition state arrangement of **6** to yield **7** (83%; dr >95:5).[9]



The bidentate $MgBr_2$ provides a mild Lewis acid which is compatible with a number of acid-sensitive protecting groups. Additionally, we have found no evidence for α-epimerization of sensitive starting aldehydes of entries 2−5 and 6 under these conditions. Reactions that were run to 50% completion led to the reisolation of starting aldehyde without loss of optical purity.[10] Similarly, nonracemic *cis*-epoxide of entry 7 is not affected despite reduced stereocontrol observed in this reaction.

To broaden the scope of our study, several simple aldehydes (entries 8−12) have also been examined. Reactions are accelerated by the use of boron trifluoride etherate, and Felkin−Anh addition is favored in chiral, racemic examples which contain α-alkyl/aryl substitution delivering the 3,4-*anti*-4,5-*syn*-stereochemistry (entries 10 and 11). Diastereomeric ratios were determined from NMR spectra of the initial product mixtures, and subsequently, major products were purified using flash chromatography.

The unambiguous assignment of stereochemistry in **7** is based on an X-ray diffraction study,[11] confirming the determinations of a series of NMR experiments. Distinctive similarities of the proton NMR spectra of products **3** and **7** and entries 1−7 display characteristic 3,4-*anti*-stereochemistry (J = 6−7 Hz). In the case of **7**, as well as the adducts of entries 1, 3, 4, and 8−12, this relationship was established by conversion to the cyclic *cis*-acetonides. Treatment with 2,2-dimethoxypropane and catalytic protic acid led to protodestannylation and exchange of MOM ethers, yielding the five-membered acetonides for ^{1}H NMR characterizations. Observed ^{1}H chemical shifts for methyl signals of *trans*-substituted acetonides document similar electronic environments due to facile ring inversion, whereas *cis*-substituted ketals, which are produced from our major products, display widely distinguished methyl singlets.[12] In addition, the chirality of the pure, nonracemic homoallylic alcohols obtained in entries 2−7 was assigned by modified Mosher ester analysis.[13] Finally, the racemic adducts of

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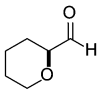
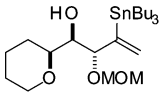
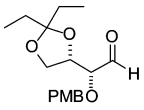
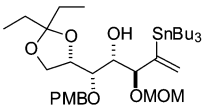
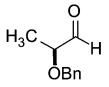
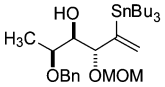
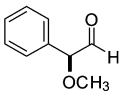
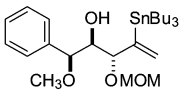
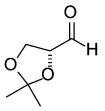
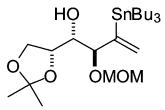
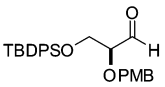
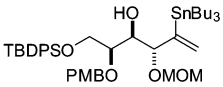
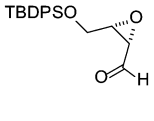
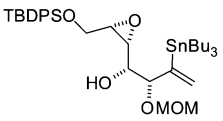
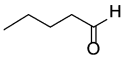
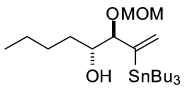
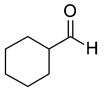
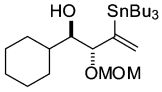
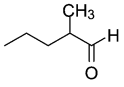
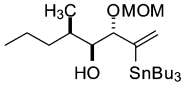
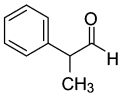
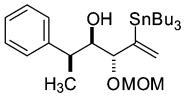
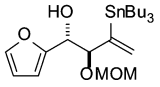
Table 1. Examples of S_E' Allylation

Entry	Aldehyde	Major Product	Ratio	Yield
1			>95:5[a]	84%
2			>95:5[a]	85%
3			>95:5[a]	82%
4			>95:5[a]	81%
5			90:10[a]	81%
6			>95:5[a]	82%
7			67:33[a]	71%
8			>95:5[b]	86%
9			90:10[b]	80%
10			80:20[b]	81%
11			93:7[b]	82%
12			72:28[b]	82%

[a] Reactions carried out under Ar atmosphere in CH_2Cl_2 at −78 °C with $MgBr_2 \cdot OEt_2$ (2 equiv) for 6 h. [b] Reactions carried out under Ar atmosphere in CH_2Cl_2 at −78 °C with $BF_3 \cdot OEt_2$ (1.1 equiv) for 2 h.

entries 10 and 11 were identified by the consistency of comparisons for proton NMR coupling constants with the careful analysis of related stereotriads pertaining to the elucidation of AAL toxin T_A by Kishi and co-workers.[14]

In conclusion, the bis-stannylation of 1-(methoxy)methoxyallene provides a reactive and fully functionalized derivative for stereocontrolled allylations. In the case of α-alkoxyaldehydes, this methodology is highly effective for bond construction of a stereotriad bearing the 3,4-*anti*-4,5-*syn*-relationship of alkoxy and hydroxy substituents. Applications to natural product synthesis are underway.

Acknowledgment. We thank the National Institutes of Health (GM42897) for support of this research.

Supporting Information Available: Procedures for allylation reactions and preparation of **2**; characterization data of **2**, **3**, **7**, major products of Table 1 and vinylic iodide ***i***; ^1H and ^{13}C NMR spectra of **2**, **3**, **7** and products of Table 1 (58 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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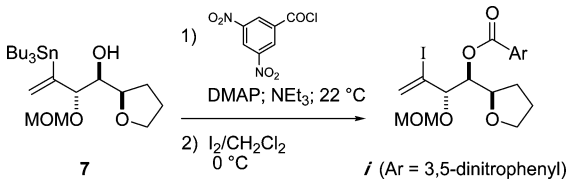
(9) For a review of the area, see: Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(10) Optical purity of recovered aldehyde was established by DIBAL reduction and subsequent Mosher ester analysis. For leading references, see: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Domingos, J. L. O.; Lima, E. C.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2313. (c) Santaniello, E.; Casati, S.; Ciuffreda, P.; Gamberoni, L. *Tetrahedron: Asymmetry* **2004**, *15*, 3177.
(11) To obtain suitable crystalline material, compound **7** was converted into the benzoate ***i*** as shown. Crystal data for ***i*** (Ar = 3,5-dinitrophenyl): colorless needle, (mp 131−132 °C) 0.12 × 0.12 × 0.10 mm, $C_{17}H_{19}IN_2O_9$, M = 522.24, monoclinic, space group $P2_1/c$, a = 13.1326(16) Å, b = 5.8396(8) Å, c = 26.555(3) Å, β = 91.813(4)°, V = 2035.5(4) Å^3, T = 123(2) K, Z = 4, ρ_{calcd} = 1.704 Mg m^{-3}, μ = 1.625 mm^{-1}, $2\theta_{max}$ = 55.08, Mo Kα (λ = 0.71073). A total of 43925 reflections were measured, of which 4692 were independent (R_{int} = 0.1479). Final residuals were $R1$ = 0.0852 and $wR2$ = 0.1715 (for 4065 observed reflections with $I > 2\sigma(I)$, 263 parameters, 0 restraints) with GOF = 1.368, and largest residual peak 1.265 e Å^{-3} and hole −2.192 e Å^{-3}. The C_4H_7O ring is disordered over two positions. 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-277461.



7 ***i*** (Ar = 3,5-dinitrophenyl)

(12) For *cis*-disubstituted acetonides, the chemical shift difference of the observed methyl singlets (^1H NMR) is greater than 0.12 ppm. For recent examples, see: (a) Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997. (b) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077. (c) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843.
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(14) The 3,4-*anti*-4,5-*syn*-stereochemistry of the major products of entries 10 and 11 displays the expected ^1H NMR coupling constants (J_{C4-H} = 3.6 and 7.2 Hz) as recorded by: Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995.

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