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Highly Diastereoselective Synthesis of Propargylic 1,2-*anti*-Diol Derivatives Using α-Alkoxypropargylstannanes

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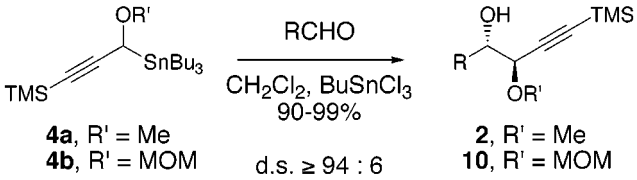
ABSTRACT



Propargylic 1,2-*anti*-diol derivatives 2 and 10 are prepared in high yield and excellent diastereoselectivity by addition of α-alkoxypropargylstannanes 4a and 4b to aldehydes in the presence of $BuSnCl_3$. We also introduce the use of KF on Celite as a convenient and mild reagent for removal of the organotin waste products of these reactions.

In connection with an ongoing problem in natural products synthesis, we needed to accomplish the *anti*-γ-methoxypropargylation of an aldehyde (Figure 1). The reactions of aldehydes with allenylmetal reagents have been extensively developed for the synthesis of homopropargylic alcohols.[1−3] Especially noteworthy are Marshall's elegant studies and synthetic applications of chiral allenyltin reagents.[1,2,4,5] However, a general, highly diastereoselective procedure for synthesis of *anti*-propargylic diol derivatives such as **2** is currently unavailable. Epsztein demonstrated in the 1970s that γ-alkoxyallenyl zinc reagents give the targeted propargylic *anti* diol monoethers with moderate selectivity (≤4:1),[6] and more recently Yamamoto reported that γ-alkoxyallenyltitanium reagents give the *anti* diol derivatives with 88:12 to 95:5 selectivity.[7] However, the selectivity of this process was less than what we hoped to achieve in our projected total synthesis. Recognizing the facility with which propargyl stannanes isomerize to allenylstannanes under Lewis acidic conditions,[5,8] we anticipated that propargyl stannane **4a** might serve as a suitable precursor to the γ-alkoxyallenylstannane **5a** needed for synthesis of **2**. Indeed, Yamamoto has demonstrated that the α-alkoxypropargylstannane **6** cyclizes upon treatment with $SnCl_4$ to give the *anti*-β-hydroxypropargyl ether **8** with excellent selectivity,

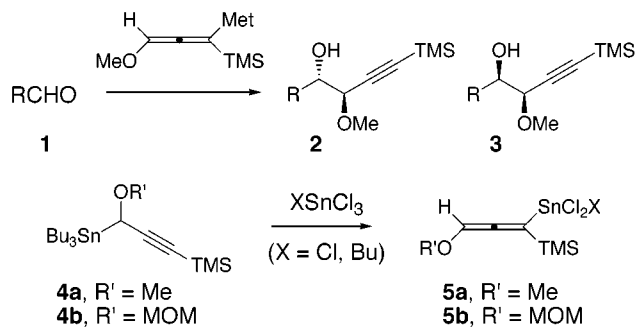


Figure 1.

(1) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 403.
(2) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(3) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 81.
(4) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.
(5) Marshall, J. A.; Yu, R. H.; Perkins, J. *J. Org. Chem.* **1995**, *60*, 5550.
(6) Mercier, F.; Epsztein, R.; Holand, S. *Bull. Soc. Chem. Fr.* **1972**, 690.
(7) Ishaguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.
(8) Guillerm, G.; Meganem, F.; LeQuan, M.; Brower, K. B. *J. Organomet. Chem.* **1974**, *67*, 43.

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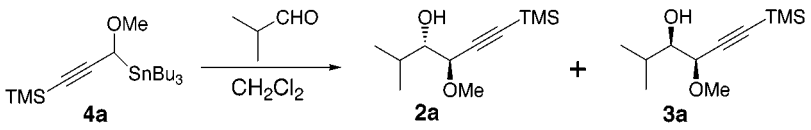
Table 1. Reaction of α-Methoxy Propargylstannane **4a** and Isobutyraldehyde



entry	equiv **4a**	Lewis acid (equiv)	method[a]	temp	workup	yield[b] *(%)*	selectivity **2a**:**3a**[c]
1	1.0	$SnCl_4$ (1.0)	A	−78 → 0 °C	Et_3N or $KF_{(aq)}$	25−66	90−94:10−6
2	1.0	$SnCl_4$ (1.0)	B	−78 °C	Et_3N	0	
3	1.0	$SnCl_4$ (1.0)	C	−78 → 0 °C	NA	0	
4	1.0	$BuSnCl_3$ (1.0)	A	−78 → 0 °C	Et_3N	36	nd
5	1.0	$BuSnCl_3$ (1.0)	B	−78 → 0 °C	$KF_{(aq)}$	56	nd
6	1.0	$BuSnCl_3$ (1.0)	A	−78 → 0 °C	KF/Celite	71[d]	nd
7	1.2	$BuSnCl_3$ (1.2)	A	−78 → 0 °C	KF/Celite	93−96	97:3
8	1.2	$BuSnCl_3$ (1.2)	A	−78 → 0 °C	$KF_{(aq)}$	79	nd
9	1.3	$BuSnCl_3$ (1.3)	A	−78 → 0 °C	KF/Celite	85[d]	nd
10	1.5	$BuSnCl_3$ (1.5)	A	−78 → 0 °C	KF/Celite	83[d]	nd
11	2.0	$BuSnCl_3$ (2.0)	A	−78 → 0 °C	KF/Celite	93[e]	97:3

[a] Method A: A solution of the Lewis acid (1.0 M in CH_2Cl_2) was added dropwise to a −78 °C mixture of isobutyraldehyde and **4a** in CH_2Cl_2. Method B: A solution of the Lewis acid (1.0 M in CH_2Cl_2) was added dropwise to a −78 °C solution of **4a** in CH_2Cl_2 followed by addition of isobutyraldehyde. Method C: A solution of aldehyde and **4a** was added to a cooled solution of $SnCl_4$. [b] Combined yield of products after silica gel chromatography, unless noted otherwise. [c] Product ratios determined by ^1H NMR analysis of the crude product. [d] Yield of HPLC purified **2a**. [e] Isolated yield of **2a**.

presumably by way of the allenyltrichlorostannane intermediate **7** (Figure 2).[9] We report herein our studies of the γ-alkoxypropargylation of aldehydes by use of the in situ generated allenylstannane reagents **5a** and **5b** (X = Bu) and demonstrate that the targeted *anti* propargylic diol monoethers can now be prepared consistently with outstanding diastereoselectivity (17:1 to ≥50:1 ds) with a range of aldehyde substrates.

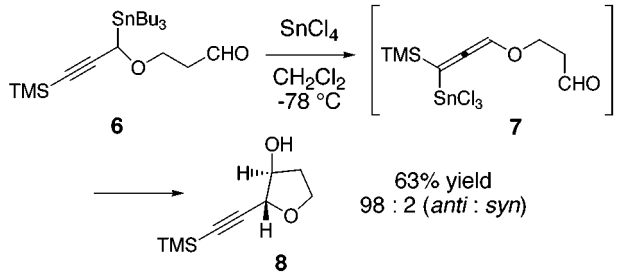


Figure 2.

α-Alkoxypropargylstannanes **4a** and **4b** were prepared by deprotonation of propargyl ethers **9a** and **9b** with *t*-BuLi followed by transmetalation with zinc chloride according to Zweifel's procedure (see Figure 3).[10] The intermediate allenylzinc species were then treated with Bu_3SnCl to give the targeted propargylstananne reagents in 82−84% yield and with only trace amounts of the allenylstannane regioisomer. Although **4a** has been previously synthesized by treatment of the propargyllithium intermediate with Bu_3SnCl,[11] we were not able to obtain isomerically pure propargylstannane by using this procedure.[12]

The reaction of **4a** and isobutyraldehyde was studied in some detail to define conditions for the α-alkoxypropargylation reaction (Table 1). Initial experiments were performed by addition of $SnCl_4$ (1 equiv) to a mixture of **4a** and isobutyraldehyde at −78 °C (entry 1). Although this reaction displayed good selectivity for the *anti* diastereomer **2a**,[13] the isolated yields were moderate and irreproducible. The order of addition of the reagents also proved crucial: if $SnCl_4$ was added to **4a** followed by the aldehyde, or to a mixture of **4a** and aldehyde, **2a** and **3a** were not obtained (entries 2 and 3). Since the reaction mixtures discolored and a precipatate formed upon addition of the $SnCl_4$ to **4a**, we reasoned that propargylstannane **4a** is not stable to $SnCl_4$. However, when we switched to $BuSnCl_3$[14] as the Lewis acid, the yields and selectivity were greatly improved (entries 4−11).

Although we were encouraged by these initial results (entries 4 and 5), separation of the major product **2a** from the organostannane byproducts proved difficult, and the

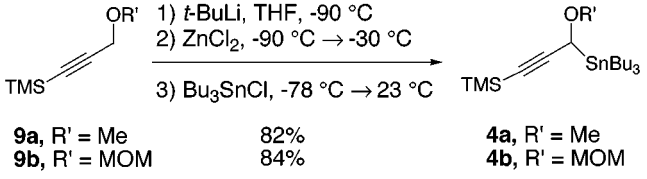


Figure 3.

(9) Kadota, I.; Hatakeyama, D.; Seki, K.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3059.
(10) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.
(11) Anies, C.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1996**, *37*, 5519.

yields sometimes varied. Of the several reported methods for removing tin wastes from reactions,[4,15−20] we tried treating the ether extracts with Et_3N[4] and stirring the extracts with aqueous KF.[15,16] Although these methods were generally successful, the large amount of precipitate/solid residue formed in both procedures was cumbersome and in some cases the product **2a** still contained alkyltin derived byproducts after chromatographic purification. Because of these problems, we developed an alternate workup procedure for removal of the organotin wastes.

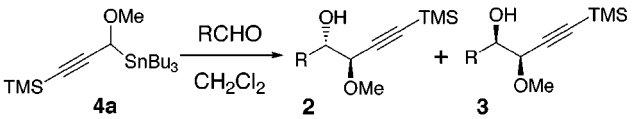
We reasoned that a solid-supported fluoride source could be a useful reagent for removal of tin residues, because the solid support would increase the surface area relative to solid KF or to biphasic extraction mixtures such as ether/aqueous KF. Potassium fluoride on Celite has been used as a catalyst for alkylations[21] and intramolecular Michael additions[22] but to the best of our knowledge has not been used for the removal of organotin wastes. The KF/Celite reagent was prepared according to the literature[21] and dried under vacuum. We were delighted to find that stirring the crude ether extracts from the reaction of **4a** and isobutyraldehyde with KF/Celite for 1 h resulted in the removal of the majority of the organotin wastes as determined by TLC analysis. Filtration of the solid gave the crude product with substantially less organotin residues as compared to previous methods. Purification of the crude material by silica gel chromatography yielded **2a** free of organotin impurities.

Further optimization of the γ-alkoxypropargylation reaction using the new workup procedure (Table 1, entries 7−11) established that only a slight excess of **4a** and $BuSnCl_3$ are necessary for **2a** to be obtained in excellent yield and diastereoselectivity. A direct comparison of the KF/Celite workup (93% yield, entry 7) versus aqueous KF workup (79% yield, entry 8) showed that the KF/Celite procedure was superior in terms of yield and convenience.[23] Analysis of these reactions by TLC revealed that the carbonyl addition did not occur below −40 °C, so all subsequent experiments were performed starting at ca. −50 °C (see Table 2).

With an optimized procedure in hand for perfoming the *anti*-γ-alkoxypropargylation reaction, we explored the reactions of **4a** with other aldehydes (Table 2). These reactions proceeded in excellent yield and diastereoselectivity. The least selective substrate in this exploratory study was crotonaldehyde, which gave products of 1,2-carbonyl addition in 96% yield with 96:4 diastereoselectivity. All other substrates gave selectivities in the 97−98% ds level. These reactions were slightly less selective when performed in less polar solvents such as toluene or hexane (see footnote d in Table 2).

It was also of interest to develop a reagent that contained a readily removable oxygen protecting group so that we could access 1,2-*anti* diol units. Initial attempts using propargyl silyl ethers were thwarted by a retro-Brook rearrangement[24] that ensued when the *O*-silyl propargyl ethers were treated with strong base. However, synthesis of the MOM ether derivative **4b** was straightforward (Figure 3), and the reactions of this reagent with a representative set of aldehydes proceeded in high yield and with excellent selectivity (Table 3). The selectivity realized by using reagent **4b** is especially noteworthy since the additions of the corresponding allenylzinc reagent showed lower diastereoselectivity (4:1 to 17:1 in the best case) and yield (77−86%).

Table 2. Reactions of α-Methoxy Propargylstannane **4a** with Aldehydes[a]

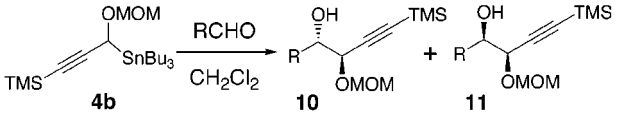


4a 2 3

RCHO	products	yield[b] (%)	2:3[c]
isobutyraldehyde	**2a**,**3a**	96	97:3
benzaldehyde[d]	**2b**,**3b**	96	97:3
crotonaldehyde	**2c**,**3c**	96	96:4
hydrocinnamaldehyde	**2d**,**3d**	98	97:3
pivaldehyde	**2e**,**3e**	96	>98:2

[a] A −50 °C solution of **4a** (1.2 equiv) and the aldehyde in CH_2Cl_2 was treated dropwise with a 1.0 M solution of $BuSnCl_3$ (CH_2Cl_2) followed by warming to 0 °C. [b] Combined product yield after silica gel chromatography. [c] Product ratios determined by ^1H NMR analysis of the crude product. [d] Reaction was performed in toluene and hexane as solvent and provided 95:5 and 96:4 mixtures of diastereomers **2b** and **3b**, respectively.

Table 3. Reactions of α-Methoxymethyl Propargylstannane **4b** with Aldehydes[a]



4b 10 11

RCHO	products	yield[b] (%)	10:11[c]
isobutyraldehyde	**10a**,**11a**	95	98:2
benzaldehyde[d]	**10b**,**11b**	97	97:3
crotonaldehyde	**10c**,**11c**	90	94:6
hydrocinnamaldehyde	**10d**,**11d**	98	96:4
pivaldehyde	**10e**,**11e**	91	>98:2

[a] Reactions were performed as described in Table 2. [b] Combined product yield after silica gel chromatography. [c] Product ratios determined by ^1H NMR analysis of the crude product.

Attempts to extend this methodology to α-alkoxypropargylstannane **12** were unsuccessful (Figure 4). These reactions did not proceed to any significant extent, and we

(12) We have recently found that mixtures of propargyl- and allenylstannanes give essentially the same results in $BuSnCl_3$-promoted reactions with aldehydes.

(13) The stereochemistry of compounds **2a**,**b** and **3a** were assigned by ozonolysis of the acetylene to the carboxylic acid followed by reduction of the acid to the diol and conversion to the acetonide. ^1H NMR and NOE analysis confirmed the stereochemistry of the acetonide derivatives. The stereochemistry of all other compounds was assigned using Hoffman's analysis of ^1H NMR chemical shifts in 1,2-diol systems (Landmann, B.; Hoffmann, R. W. *Chem. Ber.* **1987**, *120*, 331). Authentic samples of the *syn* disatereomers were obtained by addition of the lithiated **9a** and **9b** to the corresponding aldehydes.

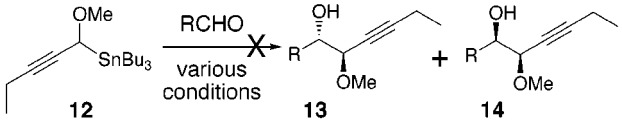


Figure 4.

could not isolate or detect the desired products **12** or **13** under several sets of reaction conditions.

Because the intermediate allenylstannanes **5a** and **5b** (generated in situ from the propargylstannanes **4a** and **4b**) are racemic, it was not obvious at the outset that these reagents would function well in reactions with chiral, nonracemic aldehydes. Recognizing that an opportunity existed for kinetic resolution of the racemic reagent in a reaction with a chiral aldehyde,[25,26] we examined the *anti*-γ-methoxypropargylation of aldehyde **15**.[27] The data summarized in Figure 5 suggest that one enantiomer of the racemic reagent **4a** reacts with **15** at a faster rate than the other enantiomer, as diastereoselectivity of 4:1 (33% yield) was achieved when 1.2 equiv of **4a** was employed, 8:1 (83% yield) with 2.5 equiv of the reagent, and 20:1 with 5 equiv of **4a**. Isomerically pure **16** was obtained in 84% yield from this experiment. Removal of the alkynyl TMS group by treatment of **16** with K_2CO_3 in MeOH at 23 °C (1 h) then provided the terminal alkyne **17** in 89% yield. Alkyne **17** is a key intermediate in our total synthesis of bafilomycin A_1,[28] and this sequence thus constitutes a significant improvement of our synthesis of this material. We anticipate that **17** will

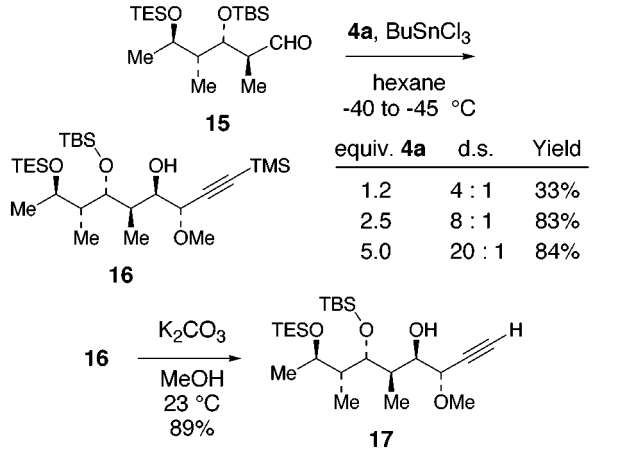


Figure 5.

serve a similar role in our ongoing total synthesis of formamicin.[29]

In summary, we have developed a highly diastereoselective procedure for the synthesis of propargyl 1,2-*anti*-diol derivatives using the $BuSnCl_3$-promoted addition of α-alkoxy propargylstannane reagents to aldehydes and have introduced the use of KF/Celite as a convenient method for the removal of organotin residues from the reaction mixtures. We have also established that racemic reagent **4a** undergoes a highly diastereoselective reaction with chiral aldehyde **15**, presumably via a kinetic resolution process. Further applications of this methodology will be reported in due course.

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Supporting Information Available: Experimental procedures for synthesis of α-alkoxypropargylstannanes **4a**,**b**; representative procedure for the additions of **4a**,**b** to aldehydes; tabulated spectroscopic data for *anti*-diol derivatives **2a**−**e**, **10a**−**e**, **16,** and **17**; and stereochemical assignments for **2a**,**b** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001.
(15) Stille, J. K.; Milstein, D. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
(16) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
(17) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.
(18) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(19) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200.
(20) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729.
(21) Ando, T.; Yamawaki, J. *Chem. Lett.* **1979**, 45.
(22) Harwood, L. M.; Loftus, G. C.; Oxford, A.; Thomson, C. *Synth. Commun.* **1990**, *20*, 649.
(23) KF/Celite does not cleave the alkynyl TMS group nor a secondary TBS ether even after 24 h.
(24) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.
(25) Poisson, J.-F.; Normant, F. H. *J. Am. Chem. Soc.* **2001**, *123*, 4639.
(26) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 6246.
(27) The details of the synthesis of aldehyde **15** will be reported elsewhere.
(28) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 165.
(29) Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 453.