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Chiral α,β-Dialkoxy- and α-Alkoxy-β-aminostannanes: Preparation and Copper-Mediated Cross-Coupling

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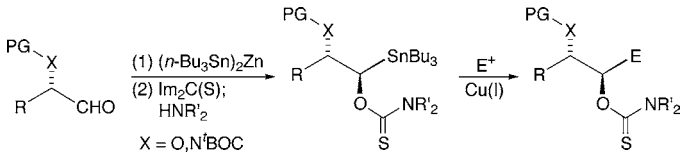
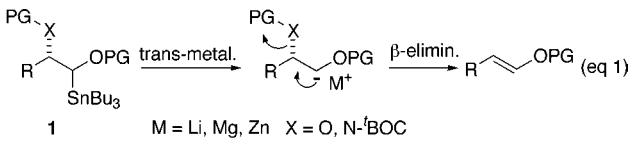
ABSTRACT



Addition of Zn(*n*-$Bu_3Sn)_2$ to prochiral aldehydes affords *anti*-α,β-dialkoxy- and *anti*-α-alkoxy-β-aminostannanes in good yield (up to 77%) and excellent diastereoselectivity (up to 98% de). *syn*-Isomers are accessed from the initial adducts via Mitsunobu inversion/saponification. The corresponding thionocarbamates undergo mild Cu(I)-mediated cross-coupling with a variety of organic halides, inter alia, allylic, cinnamylic, propargylic, and acetylenic, with retention of configuration.

α-Alkoxyalkylstannanes have received broad acceptance as convenient precursors to configurationally stable α-alkoxy-[1] and α-aminoalkyl anions,[2] as well as cuprates.[3] Comparable transmetalations with α,β-dialkoxyalkylstannanes (**1**, X = O) and α-alkoxy-β-aminoalkylstannanes (**1**, X = N^{t}BOC), however, are thwarted by facile β-elimination (eq 1).[4]



Herein, we report the facile exchange of thionocarbamate-substituted **1** with Cu(I) salts and subsequent high-yield cross-coupling to various organic halides with retention of configuration.[5] Additionally, we describe a practical, diastereoselective preparation of chiral *syn*- and *anti*-**1** from readily available precursors.[6]

Addition of the lithium or magnesium salt of *n*-tributylstannane under a variety of conditions to prochiral aldehyde (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) generated a

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(1) (a) Smyj, R. P.; Chong, J. M. *Org. Lett.* **2001**, *3*, 2903−2906. (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201−1202. (c) Sawyer, J. S.; MacDonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376−3377.

(2) (a) Ncube, A.; Park, S. B.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3625−3636. (b) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 345−349.

(3) (a) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron Lett.* **1987**, *28*, 3911−3914.

(4) Configurationally fixed anions and copper reagents have been prepared from α,γ-dialkoxyalkylstannanes: Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491−5493.

(5) Thionocarbamates are useful alcohol protective groups: Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755−4758.

(6) Synthesis of chiral α-hydroxyalkylstannanes by asymmetric reduction of acylstannanes: (a) Chan, P. C. M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584−5586. (b) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657−1660.

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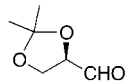
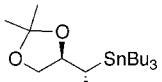
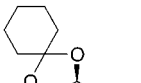
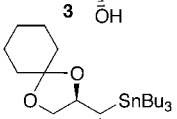
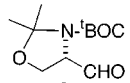
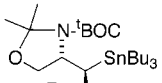
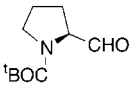
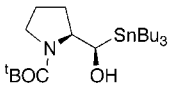
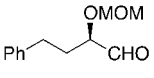
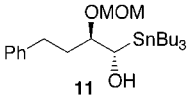
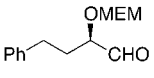
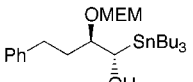
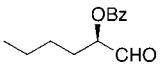
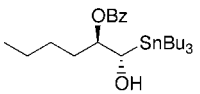
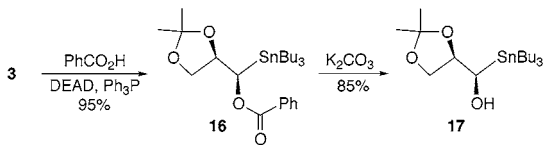
mixture of *syn*- and *anti*-adducts.[7] In sharp contrast, zinc bis(*n*-tributylstannane) afforded the *anti*-adduct **3**[8,9] in good yield and with very high diastereoselectivity (Table 1).[10] The latter result is consistent with addition to the carbonyl following the nonchelation, Felkin model.[11] Cyclohexylidene **4**,[12] oxazolidine **6**,[13] and pyrrolidine **8**[14] behaved analogously to **2**, leading predominately to *anti*-adducts **5**, **7**, and **9**, respectively. It was gratifying that the results with acyclic α-hydroxyaldehydes were also satisfactory, provided good coordinating substituents were present, e.g., MOM ether **10**[15] to **11** and MEM ether **12** to **13**. Some loss of stereospecificity occurs when esters are used, as evident in the conversion of **14**[16] to **15**. Because the adducts were somewhat labile, they were typically utilized in the next step with a minimum of delay.

Table 1. Preparation of α,*β*-Dialkoxy- and α-Alkoxy-*β*-aminostannanes

entry	aldehyde	adduct	yield (%)	de (%)[a]
1	 **2**	 **3**	72	98
2	 **4**	 **5**	77	98
3	 **6**	 **7**	74	98
4	 **8**	 **9**	70	95
5	 **10**	 **11**	68	98
6	 **12**	 **13**	75	98
7	 **14**	 **15**	66	92

[a] Determined by NMR analysis of Mosher ester.

Access to the corresponding *syn*-adducts was achieved by the Mitsunobu inversion/deprotection sequence embodied in the transformation of **3** into **17** via benzoate **16** (eq 2).



(eq 2)

(7) Review of organometallic additions to aldehyde **2**: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447−488.

(8) Representative spectral/physical data for **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87−0.96 (m, 15H), 1.28−1.35 (m, 6H), 1.39 (s, 3H), 1.43 (s, 3H), 1.48−1.54 (m, 6H), 1.99−2.01 (m, 1H), 3.83−3.88 (m, 1H), 3.92−3.97 (m, 1H), 4.19−4.21 (m, 1H), 4.30−4.36 (m, 1H); MS *m*/*z* 422 (M^+); $[\alpha]^{25}_D$ 11.9° (*c* 1.65, $CHCl_3$). Representative spectral/physical data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87−0.94 (m, 15H), 1.29−1.63 (m, 22H), 2.01−2.12 (m, 1H), 3.84 (t, 1H, *J* = 7.4 Hz), 3.94 (t, 1H, *J* = 7.35 Hz), 4.17−4.25 (m, 1H), 4.30−4.36 (m, 1H); MS *m*/*z* 462 (M^+). Representative spectral/physical data for **17**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89−0.97 (m, 15H), 1.30−1.36 (m, 6H), 1.37 (s, 3H), 1.44 (s, 3H), 1.48−1.55 (m, 6H), 1.82 (d, 1H, *J* = 6.7 Hz), 3.75 (t, 1H, *J* = 7.30 Hz), 3.91−3.96 (m, 2H), 4.39 (q, 1H, *J* = 6.4 Hz). Representative spectral/physical data for **20**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 9H, *J* = 7.3 Hz), 0.95 (t, 6H, *J* = 7.5 Hz), 1.24−1.34 (m, 9H), 1.39 (s, 3H), 1.42−1.54 (m, 6H), 3.10 (s, 3H), 3.35 (s, 3H), 3.62−3.66 (m, 1H), 4.07−4.11 (m, 1H), 4.44−4.54 (m, 1H), 4.64−5.72 (m, 1H); $[\alpha]^{25}_D$ 25.75° (*c* 2.36, $CHCl_3$). Representative spectral/physical data for **24**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 3H), 1.41 (s, 3H), 2.47−2.51 (m, 2H), 3.09 (s, 3H), 3.35 (s, 3H), 3.88 (dd, 1H, *J* = 6.0, 8.4 Hz), 4.03 (dd, 1H, *J* = 6.8, 8.4 Hz), 4.26−4.31 (m, 1H), 5.05−5.13 (m, 2H), 5.63−5.68 (m, 1H), 5.75−5.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.33, 26.61, 35.16, 37.93, 43.09, 66.40, 76.31, 80.11, 109.82, 118.29, 133.40, 187.74; MS *m*/*z* 259 (M^+); $[\alpha]^{25}_D$ = −17.56° (*c* 1.97, $CHCl_3$). Representative spectral/physical data for **34**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 3H), 1.38 (s, 3H), 1.90−1.97 (m, 4H), 2.35−2.42 (m, 2H), 2.71 (t, 2H, *J* = 7.8 Hz), 3.46−3.63 (m, 2H), 3.69−3.82 (m, 3H), 3.99 (dd, 1H, *J* = 6.0, 8.4 Hz), 4.23−4.31 (m, 1H), 5.44−5.53 (m, 1H), 5.79−5.89 (m, 1H), 6.01−6.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.74, 25.44, 25.82, 26.54, 34.42, 35.49, 48.06, 52.37, 66.08, 77.68, 80.03, 109.98, 125.17, 126.07, 128.51, 128.75, 135.52, 141.75, 184.44; $[\alpha]^{25}_D$ = −11.93° (*c* 0.62, $CHCl_3$). Representative spectral/physical data for **36**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.41 (s, 3H), 1.79−1.87 (m, 2H), 2.34−2.40 (m, 2H), 2.64 (t, 2H, *J* = 8.0 Hz), 2.97 (s, 6H), 3.72 (dd, 1H, *J* = 6.8, 8.0 Hz), 4.12 (dd, 1H, *J* = 6.4, 8.0 Hz), 4.62−4.68 (m, 1H), 5.33−5.40 (m, 1H), 7.14−7.20 (m, 3H), 7.23−7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.07, 26.89, 29.79, 34.79, 35.43, 37.03, 69.62, 74.20, 91.90, 98.10, 109.83, 125.95, 128.50, 128.73, 142.38, 166.36, 207.79; MS *m*/*z* 361 (M^+); $[\alpha]^{23}_D$ −5.30° (*c* 2.05, $CHCl_3$). Representative spectral/physical data for **38**: IR (neat) 1733, 1663, 1366, 1250, 1216, 1163, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24−1.32 (m, 4H), 1.35 (s, 3H), 1.40 (s, 3H), 1.42−1.53 (m, 2H), 1.54−1.62 (m, 2H), 1.81−1.97 (m, 4H), 2.24−2.34 (m, 4H), 3.32 (t, 2H, *J* = 6.8 Hz), 3.48 (t, 2H, *J* = 6.8 Hz), 3.62 (s, 3H), 3.70 (dd, 1H, *J* = 6.8, 8.4 Hz), 4.10 (dd, 1H, *J* = 6.0, 8.4 Hz), 4.59−4.65 (m, 1H), 5.28−7.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.74, 25.10, 25.88, 26.04, 26.88, 27.74, 28.76, 29.10, 34.26, 35.11, 46.24, 47.40, 51.63 69.63, 74.29, 91.68. 98.23, 109, 76, 163.76, 163.87, 174.45, 207.58; MS *m*/*z* 441 (M^+); $[\alpha]^{23}_D$ −11.60° (*c* 1.5, $CHCl_3$).

(9) The configuration of **3** was confirmed by conversion to **22**, removal of the thiocarbamate using $LiAlH_4$, and comparisons of the resultant alcohol with authentic samples of *erythro*- and *threo*-1,2-*O*-iospropylidenehex-5-ene-1,2,3-triol. The configuration of diastereomer **17** was likewise confirmed. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186−8190.

(10) **General Procedure for Preparation of α,*β*-Dialkoxy- and α-Alkoxy-*β*-amidostannanes.** *n*-Buli (2.2 mmol, 2.5 M in hexane) was added dropwise to a 0 °C solution of $(i\text{-Pr})_2NH$ (2.2 mmol) in anhydrous THF (3 mL) under an argon atmosphere. After stirring for 0.5 h, Bu_3SnH (2.2 mmol) was added neat over 10 min followed after another 0.5 h by dry $ZnBr_2$ (1.1 mmol) in THF (2 mL). The reaction mixture was maintained at 0 °C for 0.5 h, then cooled to −78 °C, and the prochiral aldehyde (1.0 mmol) in THF (2 mL) was added. After 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 8 mL). The combined ethereal extracts were washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash SiO_2 chromatography to the α-hydroxyalkylstannane adduct in 68−77% yield (Table 1). Adducts are somewhat labile and are best used immediately in the next reaction.

(11) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422−424.

(12) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585−587.

(13) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697−1700.

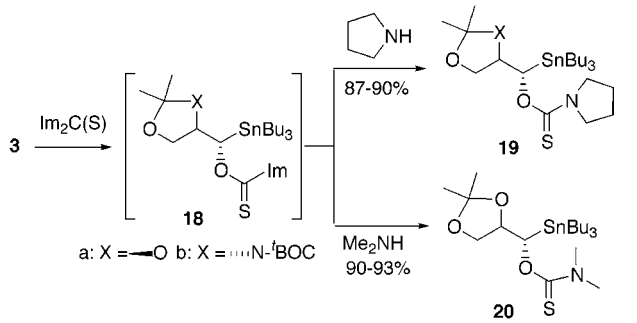
(14) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121−1123.

(15) Ogura, K.; Tsuruda, T.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1986**, *27*, 3665−3668.

(16) Kosugi, H.; Kitaoka, M.; Takahashi, A.; Uda, H. *J. Chem. Soc., Chem. Commun*. **1986**, 1268−1270.

As previously reported,[17] transition metal catalyzed cross-couplings of α-hydroxy- and α-aminoalkylstannanes are greatly facilitated by derivatization of the α-heteroatom with coordinating functionality. Thionocarbamates are especially efficacious and can stabilize the intermediate organometallic at room temperature or above.[17b] Conventional thionocarbamoylation[5] of the adducts in Table 1 using *N*,*N*-dimethylthiocarbamoyl chloride/NaH caused some equilibration, presumably via reversion to the starting aldehyde and sodium *n*-tributylstannane, then rapid recombination. Alternatively, good to excellent yields of thiocarbamate were obtained by sequential reaction with 1,1′-thiocarbonyldiimidazole and addition of a secondary amine to the intermediate thionoimidazolide.[5] This process is illustrated in the conversion of **3a**,**b** to **18a**,**b** and whence to pyrrolidine **19a**,**b** and dimethylamine **20** in good overall yields (Scheme 1).

Scheme 1. Thiocarbamoylation



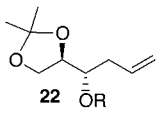
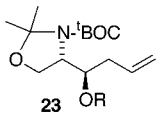
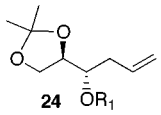
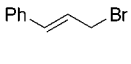
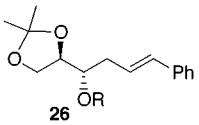
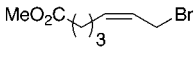
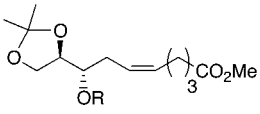
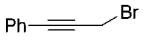
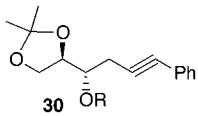
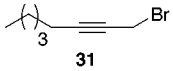
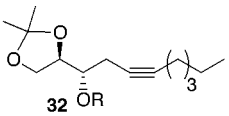
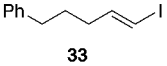
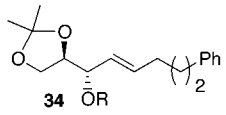
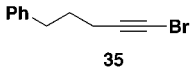
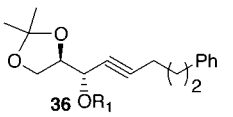
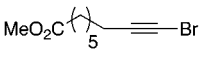
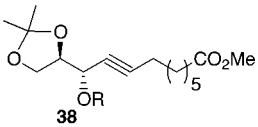
The scope of the cross-coupling was explored using **19a**,**b** or **20** and a panel of representative organic halides (Table 2).[18] All three model stannanes cross-coupled smoothly with allyl bromide (**21**) using any of several Cu(I) salts in THF at 50 °C and gave essentially identical yields of **22**, **23**, and **24**, respectively. However, the reaction rate was generally fastest with CuI.[19] Cinnamyl bromide **25** led to **26** as the sole product, whereas addition to (*Z*)-allyl bromide **27** afforded **28** accompanied by a minor amount (5%) of S_N2' adduct. Notably, no (*E*)-**28** was observed. Similar behavior was exhibited by acetylenes **29** and **31**; the former phenyl conjugated system yielded **30** only and the latter nonconjugated propargyl gave **32** and a small amount (6%) of allene. Yields of adducts at sp^2-centers, such as vinyl iodide **33** to **34**, were typically modest under our standard conditions. On the other hand, reactions at sp-centers proceeded well, e.g., **36** from **35** in 96% yield and **38** from **37** in 94% yield.

(17) (a) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982. (b) Bhatt, R. K.; Ye, J.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 3811−3814.

(18) **Cross-Coupling General Procedure.** To a stirring, room-temperature solution of α,*β*-dialkoxystannane or α-alkoxy-*β*-aminostannane (1.0 mmol) and CuI (7−10 mol %) in anhydrous THF (5 mL) was added an organic halide (1.1 mmol) in THF (1 mL) under an argon atmosphere. The resulting solution was heated at 50 °C for 3−4 h. After cooling, Et_2O (10 mL) was added, and the mixture was filtered. Evaporation ot the filtrate under reduced pressure and chromatographic purification of the residue gave the cross-coupled adduct in the indicated yield (Table 2).

(19) Best results were obtained with 7−10 mol % of Cu(I) salt. Larger quantities encouraged *β*-elimination.

Table 2. Cross-Coupling of α,*β*-Dialkoxy- and α-Alkoxy-*β*-aminostannanes

entry	thiocarb.	electrophile	adduct	yield (%)
1	**19a**	 **21**	 **22**	89
2	**19b**	**21**	 **23**	92
3	**20**	**21**	 **24**	95
4	**19a**	 **25**	 **26**	92
5	**19a**	 **27**	 **28**	89
6	**19a**	 **29**	 **30**	91
7	**19a**	 **31**	 **32**	79
8	**19a**	 **33**	 **34**	45
9	**20**	 **35**	 **36**	96
10	**19a**	 **37**	 **38**	94

R =  , R_1 = 

In summary, we report a practical diastereoselective synthesis of *syn*- and *anti*-α,*β*-dialkoxy- or α-alkoxy-*β*-aminostannanes from prochiral aldehydes, conversion of the adducts to thionocarbamates, and subsequent Cu(I)-mediated stereospecific cross-coupling with organic halides. We

anticipate this methodology will find wide utility in the construction of stereogenic centers.

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Supporting Information Available: Physical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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